Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

FOR YOUR PATIENTS WITH POST-INFECTION NEURITIS

USE

PROTAMIDE

PROMPTLY

for faster,
surer recovery
without relapse

In post-infection neuritis (following upper respiratory or virus infection), one ampul of Protamide daily for five days has been shown to produce complete recovery without relapse in 85% of patients when treatment was started during the *first week of symptoms.**

You can count on comparable results in your own practice when you

USE PROTAMIDE FIRST

for patients with post-infection neuritis, herpes zoster and certain other nerve root pain problems.

Pharmacologically safe and clinically assayed, Protamide is a sterile colloidal solution prepared from animal gastric mucosa. Due to an exclusive, unique denaturing process, protein reaction cannot be demonstrated with Protamide although it is of protein origin.

The solution is straw colored with an adjusted pH of 5.9. It is virtually painless on administration and is used intramuscularly only.

Protamide is stable at room temperature and is packaged in 1.3 cc. ampuls in boxes of ten.

*Smith, R. T., New York Med. 8:16, 1952.

A NEW EMOTIONAL STABILIZER FOR NEUROPSYCHIATRIC THERAPY

Serpasil, in a recent study,[1] proved to be a valuable supplement in the treatment of neuropsychiatric conditions, including schizophrenia, paranoid and manic states, general paresis with psychosis and some cases of depression. In many instances it eliminated the need for electroshock therapy, restraints, seclusion and barbiturate sedation.

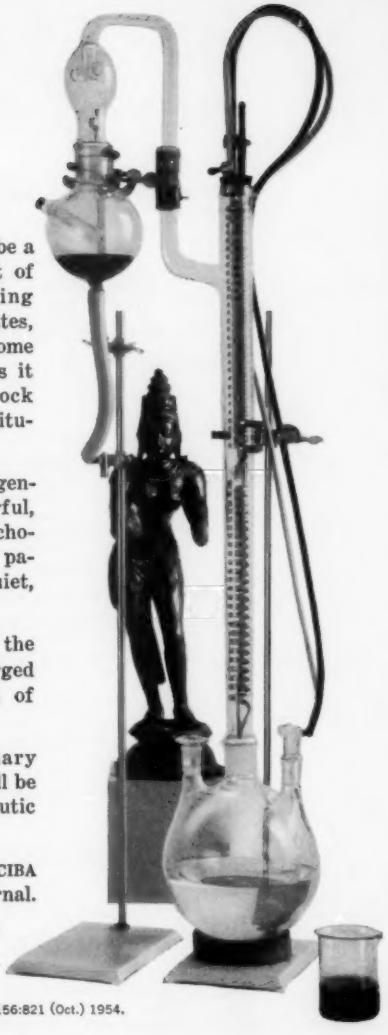
Combative, uncooperative patients in general became friendly, cooperative, cheerful, sociable and more amenable to psychotherapy under Serpasil. Hyperactive patients became sedate, noisy patients quiet, depressed patients alert.

Serpasil produced remissions in 20 of the 74 patients studied. Eight were discharged from the hospital. Long-term effects of treatment have not been determined.

If extended studies confirm preliminary findings, the authors state, Serpasil will be one of the most important therapeutic agents in the history of psychiatry.

Dosage information will be found in a CIBA advertisement elsewhere in this journal.

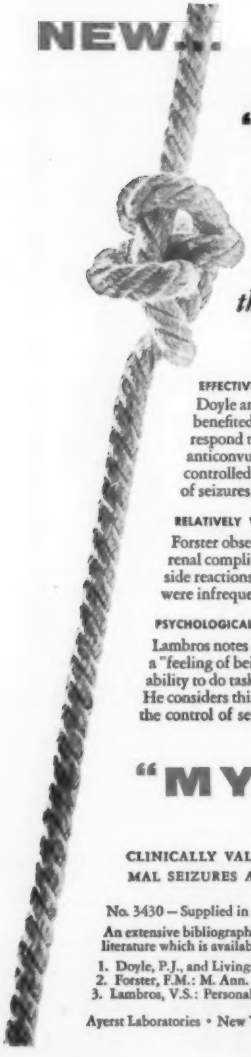
Parenteral Solution (for psychiatric use only), 2.5 mg. Serpasil per ml., 2-ml. ampuls.
Tablets, 1.0 mg. (scored), 0.25 mg. (scored), 0.1 mg.
Elixir, 0.2 mg. Serpasil per 4-ml. teaspoonful.



1. Noce, R. H., Williams, D. B., and Rapaport, W.: J. A. M. A.: 156:821 (Oct.) 1954.

Serpasil®
(reserpine CIBA)

CIBA
SUMMIT, N. J.



NEW...

"MYSOLINE"

outstandingly safe and effective anticonvulsant in the treatment of epilepsy

EFFECTIVE IN REFRACTORY CASES...

Doyle and Livingston report that 63 of 100 patients benefited from "Mysoline" therapy after they had failed to respond to maximum dosages of other anticonvulsants for at least one year. Seizures were completely controlled in 30 and the number of seizures was markedly reduced in 20.[1]

RELATIVELY WIDE MARGIN OF SAFETY...

Forster observes that "Mysoline" did not give rise to hematologic or renal complications in the 150 cases so far reported, and that side reactions, such as drowsiness and dizziness, were infrequent and usually transitory.[2]

PSYCHOLOGICALLY BENEFICIAL...

Lambros notes that over 80 per cent of 208 patients experienced a "feeling of being more alert" and showed "improvement in mental ability to do tasks which previously were burdensome." He considers this a gratifying effect of "Mysoline" therapy in addition to the control of seizures.[3]

"MYSOLINE"®

brand of Primidone

CLINICALLY VALUABLE IN THE CONTROL OF GRAND MAL SEIZURES AND PSYCHOMOTOR ATTACKS

No. 3430 — Supplied in 0.25 Gm. tablets (scored), bottles of 100 and 1,000.

An extensive bibliography supporting the value of "Mysoline" is included in the literature which is available to physicians upon request.

1. Doyle, P.J., and Livingston, S.: J. Pediat. 43:413 (Oct.) 1953.
2. Forster, F.M.: M. Ann. District of Columbia 23:137 (Mar.) 1954.
3. Lambros, V.S.: Personal Communication.

Ayerst

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

549

Volume 5 **Neurology** *Number 1*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

OFFICERS

HOWARD D. FABING, *President*

WALTER O. KLINGMAN, *President-Elect*

FRANCIS M. FORSTER, *Vice-President*

ALEXANDER T. ROSS, *Secretary*

DAVE B. RUSKIN, *Treasurer*

BOARD OF EDITORS

Editor-in-Chief: RUSSELL N. DEJONG, M.D., *Ann Arbor, Michigan*

Associate Editor: MABEL G. MASTEN, M.D., *Miami, Florida*

Editorial Board: RAYMOND D. ADAMS, M.D., *Boston, Massachusetts*

PEARCE BAILEY, M.D., *Washington, D. C.*

FRANCIS M. FORSTER, M.D., *Washington, D. C.*

ROLAND P. MACKAY, M.D., *Chicago, Illinois*

H. HOUSTON MERRITT, *New York, New York*

RICHARD B. RICHTER, M.D., *Chicago, Illinois*

AUGUSTUS S. ROSE, M.D., *Los Angeles, California*

ALPHONSE R. VONDERAHE, M.D., *Cincinnati, Ohio*

A. EARL WALKER, M.D., *Baltimore, Maryland*

ROBERT WARTENBERG, M.D., *San Francisco, California*

PAUL I. YAKOVLEV, M.D., *Boston, Massachusetts*

NEUROLOGY is published monthly at 84 South Tenth Street, Minneapolis 3, Minnesota, by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Entered as second class matter at the postoffice at Minneapolis, January 23, 1951.

To counteract extremes of emotion...

Desbutal®

DESOXYN® *to brighten the mood*

NEMBUTAL® *to relax inner tensions*

One capsule represents 5 mg. DESOXYN Hydrochloride (Methamphetamine Hydrochloride, Abbott) plus 30 mg. NEMBUTAL Sodium (Pentobarbital Sodium, Abbott). Bottles of 100 and 1,000 capsules. Abbott

502068

Upjohn

Relax

the nervous, tense, emotionally unstable:

Reserpoid *(Pure crystalline alkaloid)*

TRADEMARK FOR THE UPJOHN BRAND OF RESERPINE

Each tablet contains:

Reserpine ..... 0.1 mg.
or 0.25 mg.
or 1.0 mg.

Supplied:

Scored tablets
0.1 and 0.25 mg. in bottles of 100 and 500
1.0 mg. in bottles of 100

The Upjohn Company, Kalamazoo, Michigan

Volume 5 **Neurology** *Number 2*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

FEBRUARY 1955 • *Contents*

Maternal and Fetal Factors in the Development of Epilepsy
2. Relationship to Some Clinical Features of Epilepsy 77
BENJAMIN PASAMANICK, M.D. AND ABRAHAM M. LILIENFELD, M.D., M.P.H.

Neurologic Signs and Symptoms as Early Manifestations of Systemic Lupus Erythematosus 84
ROBERT G. SIEKERT, M.D. AND EDWARD C. CLARK, M.D.

Prostigmine-Induced Muscle Weakness in Myasthenia Gravis Patients 89
LEWIS P. ROWLAND, M.D., MARVIN C. KORENGOLD, M.D., ISRAELI A. JAFFE, M.D., LEONARD BERG, M.D. AND G. MILTON SHY, M.D.

Cerebral Metabolism of Glutamic Acid in Multiple Sclerosis 100
JOHN E. ADAMS, M.D., HAROLD A. HARPER, PH.D., GILBERT S. GORDAN, M.D., PH.D., MAXINE HUTCHIN, A.B. AND RICHARD C. BENTINCK, M.D.

Motor Epilepsy of Parietal Lobe Origin in the Monkey 108
JOSEPH G. CHUSID, M.D., LENORE M. KOPELOFF, PH.D. AND NICHOLAS KOPELOFF, PH.D.

Nature and Extent of the Biochemical Lesion in Human Epileptogenic Cerebral Cortex
An Approach to its Control 113
DONALD B. TOWER, M.D., PH.D.

NEUROLOGY, copyright 1955 by LANCET PUBLICATIONS, INCORPORATED. Title registered United States Patent Office. Louis M. Cohen, Publisher. Margaret M. Kane, Managing Editor. Maurice Wolff, Business Manager. 84 South Tenth Street, Minneapolis 3, Minnesota. ADVERTISING REPRESENTATIVES: *New York 17:* Harrison Rollins, Lee Klemmer, Bernard A. Smiler, George Doyle, John Winter, 50 East 42nd Street. Telephone: Murray Hill 2-8717. *Chicago 6:* Jay H. Herz, 20 North Wacker Drive, Suite 1921. Telephone: Central 6-4619. *San Francisco 4:* Duncan A. Scott & Co., Mills Building. Telephone: Garfield 1-7950. *Los Angeles 5:* Duncan A. Scott & Co., 2978 Wilshire Blvd. Telephone: Dunkirk 8-4151.

Contents — *Continued*

Clinical Pathologic Conference 131

Presented by DELBERT M. BERGENSTAL, M.D., CHARLES F. BARLOW, M.D. AND RICHARD B. RICHTER, M.D.

Case Report

Status Marmoratus of the Thalamus and Striatum Associated with Athetosis and Dystonia 139

MALCOLM B. CARPENTER, M.D.

Book Reviews 147

INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

Manuscripts submitted for publication (other than those read at meetings of the Academy) should be sent to Dr. Russell N. DeJong, University Hospital, Ann Arbor, Michigan. Books for review and business correspondence should be addressed to NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota. Articles dealing with the history of neurology should be sent to Dr. Webb Haymaker, Armed Forces Institute of Pathology, 7th and Independence, S.W., Washington 25, D.C. News items related to the American Academy of Neurology or to the field of neurology in general are to be sent to Dr. Pearce Bailey, 4725 Sedgwick, N.W., Washington 16, D.C.

Manuscripts are accepted for publication on condition that they are contributed solely to NEUROLOGY. They must be typewritten, double spaced, and only the original copy should be submitted. Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be glossy prints. Tables should be typed on separate sheets. The title of the article, name of author, and number of figure should be placed on the back of every illustration, and the top should be designated. Legends for figures should be typed and are not to be attached to the illustrations. If the number of illustrations or tables is excessive, the author will be asked to defray a part of the cost.

References should be designated in the text by superior number, and should be listed at the end of the article in numerical sequence. They should be typed in the following manner:

Journal reference: 1. FRANKLIN, C. R., and BRICKNER, R. M.: Vasospasm associated with multiple sclerosis, Arch. Neurol. & Psychiat. 58:125, 1947.

Textbook reference: 2. WECHSLER, I. S.: A Textbook of Clinical Neurology, ed. 3, Philadelphia, W. B. Saunders Company, 1935, pp. 194-199.

Abbreviations should follow the style of the Quarterly Cumulative Index Medicus.

Galley proofs will be sent to authors for prompt correction. There will be no charge for corrections unless excessive alterations are made. A schedule of charges for reprints will accompany the galley proof.

Lederle

Artane*

HYDROCHLORIDE

Trihexyphenidyl Hydrochloride *Lederle*

EFFECTIVE IN ALL THREE TYPES OF PARKINSONISM

POSTENCEPHALITIC • ARTERIOSCLEROTIC • IDIOPATHIC

ARTANE is usually well tolerated. It is a strong antispasmodic, yet produces fewer undesirable side effects than atropine. It exhibits many times the activity of most other synthetic drugs with atropine-like action; it does not lose effectiveness when given over long periods; and it has no deleterious effect on bone marrow function.

ARTANE is administered orally, in tablet or elixir form, three or four times daily. Dosage starts with 1 mg. the first day, gradually increased, according to response, to 6 mg. to 12 mg. daily.

ARTANE Tablets are supplied in 2 mg. and 5 mg. strengths, in bottles of 100 and 1,000. ARTANE Elixir (2 mg. per teaspoonful [4 cc.]) is supplied in 16 fluidounce and 1 gallon bottles.

*Reg. U.S. Pat. Off.

LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

PEARL RIVER, NEW YORK

REITER

THE ORIGINAL ELECTROSTIMULATORS

PRESENTS AN ADVANCED MODEL USING UNIDIRECTIONAL CURRENTS FOR EVERY ESTABLISHED TECHNIQUE.

MODEL RC-47C

- CONVULSIVE THERAPY — full range
- FOCAL TREATMENT — unilateral and bilateral convulsions
- NON-CONVULSIVE THERAPIES
- MONO-POLAR TREATMENT — non-convulsive or convulsive
- BARBITURATE COMA AND OTHER RESPIRATORY PROBLEMS
- ELECTRO-SLEEP THERAPY

Introduced about a year ago to members of the profession, MODEL RC-47C has already gained wide-spread interest and use. This model is the most versatile of all Reiter electro-stimulators. All the clinically established therapeutic techniques may be applied with this one machine. Automatic safeguards assure an amazing reduction of thrust even with an extremely high introduction of current and, in like manner, there is remarkable freedom from apnea and confusion. A new feature of MODEL RC-47C is a rugged, instantly re-set electronic timer providing stop-watch accuracy up to a full hour.

No technique employing electrical currents, muscle relaxant drugs or a combination thereof, can completely prevent undesirable effects. But techniques clinically developed for use with the Reiter "Unidirectional Currents" electrostimulators provide the means to reduce these side effects to an absolute minimum.

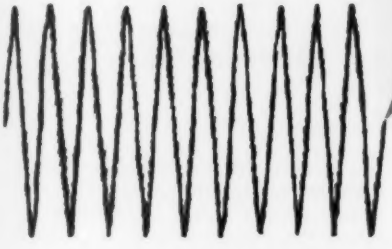
MORE THAN 125 REFERENCES IN LITERATURE AND TEXT-BOOKS.

Bibliography and literature on request.

ANNOUNCES THE FIRST OF A SERIES OF INSTRUMENTS EMPLOYING A.C. TREATMENT CURRENTS

The MOL-AC
TRADE MARK

- MINIATURE SIZE — FITS IN YOUR COAT POCKET
- LIGHTWEIGHT — ABOUT 3 LBS.
- CLINICALLY EVALUATED
- FULL POSITIVE MANUAL GLISSANDO AND TIMING
- COVERS ENTIRE VOLTAGE RANGE
- NO WARM-UP DELAYS
- INSTANTLY RE-SET
- LONG SERVICE LIFE
- MOST ECONOMICALLY PRICED

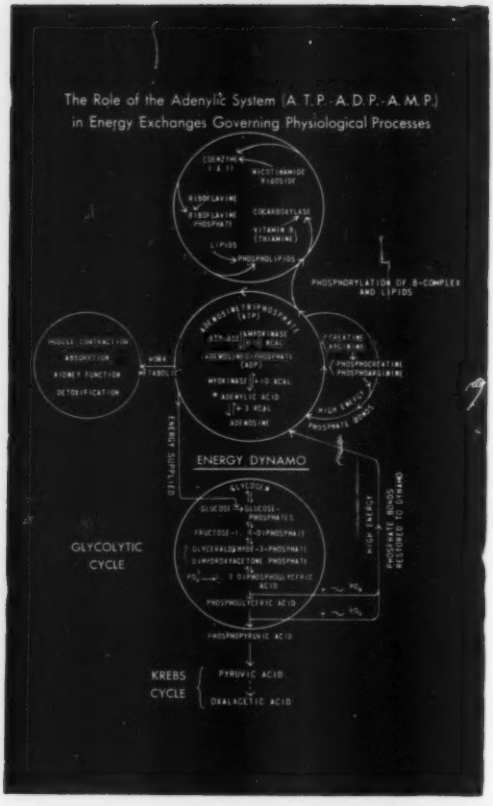


The MOL-AC is the smallest, lightest, least expensive clinically proven A.C. shock therapy instrument available to physicians. This model, the first of a series of Reiter A.C. instruments, offers the same results as other equipment many times its size, weight and price. Compactly designed to fit in a welded steel 3 x 5 inch case.

The MOL-AC provides for full positive manual control of glissando over the entire voltage range as well as a positive manual control of time. There are no complicated settings of dials, no waiting for re-setting of timing devices, no warm-up delays — just plug into ordinary A.C. house current and the MOL-AC is ready for immediate use. Only the finest components have been assembled to assure long trouble-free operation. The MOL-AC is priced at $55.00 F.O.B., New York.

REUBEN REITER, Sc.D.

38 WEST 48th STREET, ROOM 601, NEW YORK 36, N. Y.



IRONYL

THE IRON SALT OF YEAST ADENYLIC ACID

(Adenosine-3-Monophosphate)

The adenylic system is an essential factor in regulating carbohydrate metabolism and energy release in muscle and in the phosphorylation of thiamin to the biologically active coenzyme cocarboxylase.

Adenosine - 3 - monophosphate remains in the blood stream in the free state without being deaminated, acting as a constant reservoir of adenosine for the build up of A.T.P.

In cases of fatigue and exhaustion and in diseases associated with spasm and insufficient relaxation of striated muscles such as sacro-iliac, arthritis and torticollis, IRONYL® supplies adenosine-3-monophosphate as a source of muscle energy. It may be mixed in the same ampul as an injectable B complex for increasing the effectiveness of B complex therapy.

Each 1 cc. ampul of IRONYL® contains 32.4 mg. of Iron Adenylate (4.4 mg. of available iron and 28 mg. of Adenosine-3-Monophosphate). **IRONYL is supplied in boxes of 10, 25 and 100 ampuls, and in bottles of 12, 25 and 250 Sublingual Tablets.**

Available for the Clinical Investigator: **Procanyl** (Procaine Adenylate). Each 1 cc. ampul contains the equivalent of 20 mg. of procaine base (2%) and 30 mg. of adenosine-3-monophosphate.

PHYSIOLOGICAL CHEMICALS CO., INC.
3 LE FEVRE LANE
NEW ROCHELLE, NEW YORK

Reprints and Literature available on Request

Serpasil®

EFFECTIVE EMOTIONAL STABILIZER WHEN USED IN ADEQUATE DOSAGE

IF adequate doses of Serpasil are given, many neuropsychiatric patients can be emotionally stabilized, as shown in a recent study.[1]

These doses may be considered high when compared with those used in the treatment of anxiety states and hypertension, but they are absolutely required and generally well tolerated.

1. Noce, R. H., Williams, D. B., and Rapaport, W.: J.A.M.A. *156*:821 (Oct.) 1954.

If you do not have a dosage card, please clip out plan below.

---

2 / 2083M

Serpasil

DOSAGE PLAN FOR NEUROPSYCHIATRIC CONDITIONS

Serpasil in doses of 2.5 to 5.0 mg. (1 to 2 ml.) is administered intramuscularly, while oral medication is started at 1.0 mg. b.i.d. It may be necessary to repeat the injection every day or every other day for the first 2 or 3 weeks. After the first week, the oral dosage may be increased, when necessary, to three or four 1.0-mg. tablets per day. As a general rule, a maintenance dosage of one to two 1.0-mg. tablets daily is adequate after a few weeks of therapy.

SERPASIL®
(reserpine CIBA)

C I B A
SUMMIT, N. J.

Parenteral Solution (for psychiatric use only), 2.5 mg. Serpasil per ml., 2-ml. ampuls.

Tablets, 1.0 mg. (scored), 0.25 mg. (scored), 0.1 mg.

Elixir, 0.2 mg. Serpasil per 4-ml. teaspoonful.

MODEL D
Electroencephalograph

For Ruggedness, Dependability and Better Fidelity

All Steel Console

Stainless Steel dial plates and table top

No "B" batteries or wet batteries

ACCEPTED
COUNCIL ON PHYSICAL MEDICINE and REHABILITATION
AMERICAN MEDICAL ASSOCIATION

MODEL B-24
SHOCK THERAPY UNIT

Glissando or direct

The standard instrument for shock therapy

MEDCRAFT ELECTRONIC CORP.

426 GREAT EAST NECK ROAD
BABYLON, N. Y.

Designers and Manufacturers of Diagnostic and Therapeutic Equipment for the medical profession.

Telephone: MOhawk 9-2837
Cable: Medcraft Babylon NY

Upjohn

Gradual and sustained lowering of blood pressure:

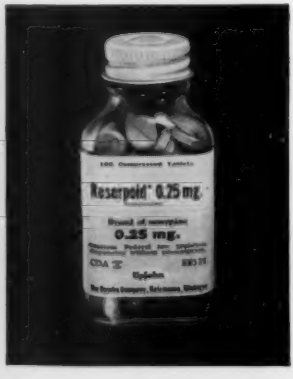
Each tablet contains:

Reserpine ..... 0.1 mg.
or 0.25 mg.
or 1.0 mg.

Supplied:

Scored tablets
0.1 and 0.25 mg. in bottles of 100 and 500
1.0 mg. in bottles of 100

The Upjohn Company, Kalamazoo, Michigan



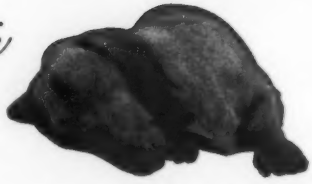
Reserpoid

TRADEMARK FOR THE UPJOHN BRAND OF RESERPINE

(Pure crystalline alkaloid)

hypnotic

prompt action



rapid elimination

clear-headed awakening

ELIXIR ALURATE

'Roche'

Available as ELIXIR ALURATE, cherry red color/ELIXIR ALURATE VERDUM, emerald green color
Each contains 0.03 Gm (½ grain) of Alurate per teaspoonful (4 cc)
in a palatable vehicle. Alurate®—brand of aprobarbital

HOFFMANN-LA ROCHE INC. • ROCHE PARK • NUTLEY 10 • NEW JERSEY

Volume 5 Neurology Number 2

Maternal and Fetal Factors in the Development of Epilepsy

2. Relationship to Some Clinical Features of Epilepsy

Benjamin Pasamanick, M.D. and Abraham M. Lilienfeld, M.D., M.P.H.

THE relationship of injuries of the brain to death, palsy, disorders in psychologic functioning, and convulsive seizures has been known since antiquity. Obstetric factors at delivery have also been accepted as causes of brain injury for centuries. These factors, mechanical in nature, caused the lacerations, hemorrhages, and asphyxias which were said to be responsible for death and cerebral dysfunction. While these relationships are undoubtedly valid, considerable warranted skepticism has been expressed concerning the frequency of such injuries and, therefore, the clinical entities for which they are responsible. In the field of epilepsy where genetic factors have been introduced to fill the gap in our knowledge, "the differences in opinion mean, of course, that the evidence at hand does not furnish conclusive proof in any direction." [1]

Since the days of Ballantyne at the beginning of this century, a number of prenatal factors have been increasingly incriminated as potentially damaging to the fetus, and within the last two decades, malnutrition, including avitaminoses, infection, anoxia, endocrine imbalance, and toxemias of pregnancy have been implicated in this fashion. All these variables in addition to the obstetric factors and prematurity had been shown not only to be interrelated but also related to neonatal mortality, stillbirth, and abortion. Recently we were led to the formulation of the concept of a *continuum of reproductive casualty,*

Presented before the American League Against Epilepsy, Washington, D.C., May 6, 1954.
From the departments of public health administration (division of mental hygiene) and epidemiology, Johns Hopkins School of Hygiene and Public Health, Baltimore.
Aided by a grant from the Foundation for Mentally Retarded and Handicapped Children of Baltimore, Maryland.

encompassing a gradation of various complications of pregnancy, delivery, and prematurity which would result in graduated cerebral damage extending all the way from death, through cerebral palsy, mental deficiency, to epilepsy, and reaching perhaps as far as the minor dysfunctions which could result in behavior disorder. As stated previously, these relationships had been shown to be valid for fetal and neonatal death and have held true for cerebral palsy.[2]

A series of epidemiologic studies examining this concept of a continuum have been completed, and in this report we would like to present a portion of the investigation devoted to epilepsy. The method, which has been described more fully in a previous report,[3] consisted of securing from certain clinics, hospitals, and institutions the names and identifying information for all cases of epilepsy born in Baltimore between 1935 and 1952. When available, clinical data was also secured, including age of onset, types of seizure, presence of associated defects such as mental deficiency, cerebral palsy, and so on, and electroencephalographic findings. All duplicate cases were discarded and the Baltimore City birth register was then searched for the birth certificates of those children born in Baltimore. For a control the next birth reported from the same place as the epilepsy case, born to a mother of the same race and age group, was obtained. From the birth certificates the following information was secured: place of birth (home delivery or name of hospital), maternal age, number of previous pregnancies, sibling deaths, and stillbirths.

For those cases and controls born in hospitals the following information concerning the mother's pregnancy and delivery was abstracted from the hospital record by a research staff member, who was not informed as to which was case or control: number of previous pregnancies, abortions, stillbirths, premature and neonatal deaths, length of labor, complications of pregnancy and labor, operative procedures, birth weight, and condition of child during the neonatal

TABLE 1

FREQUENCY OF VARIOUS ABNORMALITIES OF PRENATAL AND PARANATAL PERIODS AMONG EPILEPTIC CASES AND MATCHED CONTROLS BY RACE

Abnormality	WHITE				NON-WHITE			
	Epileptics		*Controls*		*Epileptics*		*Controls*	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
With one or more maternal complications	76	27.7	51	18.8	60	49.2	53	43.5
With two or more maternal complications	22	8.0	6	2.2	22	18.0	14	11.5
Prematurity	34	12.9	10	3.8	19	15.3	15	12.3
Prematurity without maternal complications	15	5.5	7	2.6	8	6.6	6	4.9
Abnormal neonatal conditions without prematurity or maternal complications	17	6.2	9	3.3	5	4.1	2	1.6
With one or more abnormalities of prenatal and paranatal periods	108	39.4	67	24.7	73	59.9	61	50.0
Total cases	274	—	271	—	122	—	122	—

period. If the control infant had died during the stay in the hospital, it was discarded and the next child with the same control qualifications was chosen. This was done since it was obvious that a child dying during the neonatal period could not have a chance to develop epilepsy and, therefore, could not be used to compare its experience with an experimental subject who had survived this period. In some hospital records data were not complete, so that for some specific items the groups vary slightly in size.

Five hundred sixty-four epileptic cases born in Baltimore were found and studied in the above manner. Approximately one third (33.7 per cent) were non-white. Three quarters (75 per cent) of the white and two thirds (66 per cent) of the non-white births took place in hospitals. Three per cent were products of twin pregnancies, somewhat higher than expected as compared to 1.2 per cent among the control group. Fifty-eight per cent of the white epileptics but only 50 per cent of the non-white were males.

Since the socioeconomic background of these cases could be questioned because of inclusion of clinic cases, the census tract of their residence at time of birth was obtained. This information, which permits grouping into eonomic categories, revealed that the distribution of cases and their matched controls was essentially similar with regard to socioeconomic status.

In a previous report,[3] the specific associations of complications of pregnancy and parturition, prematurity, and abnormal neonatal condition with epilepsy were presented. They are summarized in table 1. In brief, in the white epileptic group the frequency of maternal complications, prematurity, and abnormal condition at birth was significantly greater than in the control group. (Throughout this report differences will be considered statistically significant at probability levels of .05 or less.) The most important maternal complications by far were the toxemias of pregnancy and bleeding during pregnancy and labor. The most common abnormalities noted in the neonatal period were asphyxia requiring prolonged resuscitation and convulsions.

In the non-whites all differences were in the expected direction of more abnormalities among the experimental group, but not all were statistically significant. The possible reasons for this have been discussed in detail,[3] and are related to the small number in the non-white group and the very high incidence of complications of pregnancy in Negroes, requiring larger numbers for detection of differences.

A few other findings of interest might be added. When length of labor and types of operative procedures during delivery were compared, no essential differences were noted, largely eliminating these mechanical factors from consideration in the etiology of epilepsy.

Since there was some possibility that the relationship we have been discussing might be due to the presence of associated defects such as cerebral palsy and mental deficiency, the data were analyzed separately in the cases with and without these defects. The differences remained significantly greater in the epileptic group when compared to the controls, even when these defects were taken into consideration.

Since we had data available on the occurrence of epilepsy in the families of our cases, we thought it might be

fruitful to see what light might be cast on the genetic hypothesis. It is reasonable to assume that, if prenatal and paranatal factors play a significant role in the causation of epilepsy, the cases in which these factors were absent should have more epileptic parents than those cases in which these factors were present. This was not found to be true. Epilepsy was found in 4.5 per cent of the parents in all cases and 5.1 per cent of the parents in the groups with no abnormalities of childbearing.

These and similar findings make it necessary to reexamine the genetic hypothesis in epilepsy. Familial aggregation of epilepsy is not reported by all observers. Secondly, where it is found, may it not be a reflection of the occurrence of familial aggregation of the pre- and paranatal factors under discussion in this report? Prematurity, stillbirths, and neonatal deaths have been so described.[4,5] There is a suggestive positive correlation between low socioeconomic status and complications of pregnancy and parturition as well as prematurity. Some of the factors hypothecated to be etiologic, such as malnutrition and heavy work during pregnancy, are also more common in the lower socioeconomic strata. Even the greater concordance for epilepsy in monozygous twins might be explained on the basis of greater exposure to abnormal prenatal and paranatal influences. There is some validation for this hypothesis in the finding of a higher frequency of prematurity and stillbirths among identical than among fraternal twins.[6]

In this report we would like to present some of the findings concerning abnormalities during the prenatal and paranatal periods relevant to the clinical data gathered.

It has been postulated that brain injury is more likely to result in a major type of seizure than in minor types. The distribution of maternal and neonatal abnormalities according to the type of seizure is presented in table 2. (In this table and table 3 following, whites and non-whites are pooled since no differences between these two groups were discovered.) No statistically significant differences were found, and it must be assumed that as far as our data are concerned cerebral damage might be etiologic in any type of seizure.

The second set of relationships under study revolved about the concept that if brain injury were present the electro-

TABLE 2
FREQUENCY OF MATERNAL AND FETAL ABNORMALITIES AMONG EPILEPTIC CASES BY TYPE OF SEIZURE

	EPILEPTICS		
		Cases with One or More Abnormalities	
Type of Seizure	*Total*	*Number*	*Per cent*
Grand mal	207	97	46.9
Grand mal and petit mal	28	15	53.6
Grand mal and other	5	1	20.0
Petit mal	54	21	38.9
Petit mal and other	9	4	44.4
Other types	11	7	63.6
No type stated	64	24	37.5

TABLE 3
FREQUENCY OF MATERNAL AND FETAL ABNORMALITIES AMONG EPILEPTIC CASES BY ELECTROENCEPHALOGRAPHIC FINDINGS

Electroencephalographic finding	EPILEPTICS		
	Total	*Cases with One or More Abnormalities*	
		Number	*Per cent*
Normal	46	19	41.3
Abnormal—no localization	116	50	43.1
Abnormal—with localization	61	27	44.3
None listed	155	73	47.1

encephalogram was much more likely to be abnormal. In addition, it has been thought that electroencephalographic localization would be present more often under such circumstances.[7] Of the 378 cases for which hospital data was available, 221 had had electroencephalographic study. These were divided into three groups: those with normal records, those with abnormal findings but no localization, and those with abnormal findings and localized differences. These findings, when tabulated according to maternal and neonatal abnormalities (table 3), again revealed no essential differences and this hypothesis also finds no validation in our data.

This finding must be interpreted with caution because of existing differences of opinion concerning interpretation of electroencephalographic abnormalities. Unfortunately, there is little agreement among electroencephalographers concerning definitions of abnormality. The mere fact that there is an absence of abnormality in obvious cases of epilepsy emphasizes the need for investigation of the variations in electroencephalographic interpretation. Until this matter has been fully investigated, records should be interpreted cautiously, particularly with regard to drawing inferences concerning etiology.

Some workers in the field of epilepsy have felt that the earlier the onset of seizures the more likely would cerebral injury be found to be causative and that, therefore, more abnormalities prior to and during delivery should be found. In the most recent report of this impression, Smith and co-workers stated that, with respect to the patient's age at the

TABLE 4
FREQUENCY OF MATERNAL AND FETAL ABNORMALITIES BY RACE AND AGE AT ONSET OF SEIZURES

Age at onset	EPILEPTICS		
	Total	*Cases with One or More Abnormalities*	
		Number	*Per cent*
White:			
Under one year	70	36	51.4
Over one year	146	49	33.6
Non-white:			
Under one year	25	15	60.0
Over one year	91	53	58.2

first seizure, there was a progressive decline of paranatal mishaps with increasing age.[7] On analysis of our data some suggestive differences were noted. In the white group, the percentage of total abnormalities was 51.4 in children whose onset was under one year of age, as contrasted to 33.6 per cent in the groups with onset after age one. This is statistically significant at less than the .05 level and there is some indication that this clinical impression has some validity.

However, in the non-white group, this relationship is not found. The percentage of abnormalities in children with onset before one year is 60.0 and after the first year, 58.2. It is interesting to note the relatively smaller percentage of non-white children (27 per cent) with an onset during the first year when compared to the whites (48 per cent). This might be explained partially on the basis that more Negroes who are brain-injured do not survive the first year to become epileptic. This is reflected in the higher stillbirth, neonatal, and infant mortality rates among Negroes. One wonders if this is not related to the findings discussed earlier, that is, that many of the comparisons in the non-white group did not exhibit statistically significant differences.[2]

DISCUSSION

It would be comparatively safe to state that there exists more than a chance relationship between some abnormal conditions associated with childbearing and the subsequent development of epilepsy in the offspring. It might be of interest to add parenthetically that similar relationships have been discovered for mental deficiency and childhood behavior disorder and will in time be reported. We must at the same time indicate that there are quite definite limitations to the inferences which can be drawn from such retrospective studies where one secures information concerning already existing clinical entities and then searches for background data in the past. It might be concluded validly that these relationships are merely associated findings rather than causative relationships. Only anterospective studies, already underway or being planned, in which groups of infants classified according to the maternal and fetal factors implicated in this study could be followed so as to be able to really measure the risks of developing the various neuropsychiatric conditions discussed, could provide the necessary confirmatory evidence.

Despite the caution which must be exercised in drawing definitive conclusions, it must be stated that on the basis of evidence presented here and elsewhere the concept of a *continuum of reproductive casualty* appears to be a most useful one. It appears entirely rational to conceive of influences which are almost certainly lethal in some pregnancies, sublethal in others, and cause sufficient cerebral damage to result in varying degrees and types of neural dysfunction. Our data also indicate that the prenatal factors that result in nonmechanical injury such as anoxia may prove to be as important, if not more so, both quantitatively and qualitatively, as those factors which are more prone to result in mechanical trauma.

It would appear from the results of these studies that any hope for the prevention of epilepsy, in whole or in part, depends on the ability to prevent certain morbid processes during pregnancy. At present, our knowledge of the causes

of toxemias and bleeding during pregnancy is relatively insufficient for instituting preventive measures. However, there is sufficient knowledge for the prevention of malnutrition and infection during pregnancy, conditions which have deleterious influences on the fetus, and measures to prevent such conditions should be instituted. There is a need for more obstetric research in order to elucidate the etiologic factors of these conditions. Any research done in this area may provide information for further proof of the presence of the hypothesized continuum.

SUMMARY

The birth certificates and obstetric records of 564 epileptic children born in Baltimore between 1935 and 1952 showed significantly more abnormalities during pregnancy, delivery, and in the neonatal period than a similar number of matched controls. There were no differences in the number of these abnormalities among epileptic children whose parents did or did not have seizures, or according to type of seizure or electroencephalographic abnormality. In the white group, but not in the non-white group, there was a significantly higher number of abnormalities in the children whose seizures had their onset during the first year of life. Some doubt is raised as to the genetic etiology of epilepsy and a hypothesis formulated of a *continuum of reproductive casualty*. This continuum consists of brain damage incurred during the prenatal and paranatal periods as a result of abnormalities during these periods, leading to damage extending from death through cerebral palsy, mental deficiency, behavior disorder, and epilepsy.

The authors would like to express their grateful appreciation to the directors and medical record librarians of the clinics and hospitals in Baltimore, to the staffs of the Statistical Section of the Baltimore City Health Department and the Maryland State Department of Mental Hygiene, without whose cooperation this study could not have been carried out. They would also like to acknowledge the assistance of Mrs. Frances Constantinou, R.N., research assistant in the Department of Public Health Administration, in obtaining the data upon which this report is based.

REFERENCES

1. Bridge, E. M.: Epilepsy and Convulsive Disorders in Children, New York, McGraw-Hill Book Company, 1949.
2. Lilienfeld, A. M., and Parkhurst, E.: A study of the association of factors of pregnancy and parturition with the development of cerebral palsy, Am. J. Hyg. 53:262, 1951.
3. Lilienfeld, A. M., and Pasamanick, B.: The association of maternal and fetal factors with the development of epilepsy. I. Abnormalities in the prenatal and paranatal periods. J.A.M.A. 155:719, 1954.
4. Karn, Mary N., Lang-Brown, H., MacKenzie, H., and Penrose, L. S.: Birth weight, gestation time and survival in siblings, Ann. Eugenics 15: 306, 1951.
5. Gardiner, E. M., and Yerushalmy, J.: Familial susceptibility to stillbirths and neonatal deaths, Am. J. Hyg. 30:11, 1939.
6. Yerushalmy, J., and Sheerar, S. E.: Studies on twins. II. On the early mortality of like-sexed and unlike-sexed twins, Human Biol. 12:247, 1940.
7. Smith, B., Robinson, G. C., and Lennox, W. G.: Acquired epilepsy: A study of 535 cases, Neurology 4:19, 1954.

Neurologic Signs and Symptoms as Early Manifestations of Systemic Lupus Erythematosus

Robert G. Siekert, M.D. and Edward C. Clark, M.D.

ALTHOUGH systemic lupus erythematosus is a generalized disease, in the course of which neurologic symptoms or signs might be expected to occur, it has been only within recent years that the neurologic aspects have elicited much interest. In general, it has also been felt that evidence of neurologic dysfunction usually is a late accompaniment, seen only in the terminal stages of this disease. Very little has been written concerning neurologic symptoms or signs occurring early in the course of systemic lupus erythematosus.

In recent years several patients with systemic lupus erythematosus have been observed in whom neurologic abnormalities had developed prior to the time that the diagnosis of lupus erythematosus was established. Because neurologic difficulties actually may be among the first, rather than later, manifestations of systemic lupus erythematosus, it seemed of value to present the following three cases.

Case 1.—A 16 year old girl was admitted in May 1949 because of left hemiplegia, fever, and pain in the chest. Four years before admission she had had swollen and painful joints and a choreiform movement disorder. The diagnosis of "rheumatic fever with Sydenham's chorea" had been made. Two years prior to admission she had begun to experience dizzy spells. On one occasion she had had diplopia. At that time she also had a febrile illness, during which left hemiplegia suddenly developed and never abated. The cerebrospinal fluid and results of a pneumoencephalogram were said to have been normal. The sedimentation rate apparently was elevated. Dysarthria and an eruption on the face occurred six months before admission of the patient. The lesions of the face soon became purpuric and thoracic pain began. Aspiration revealed pleural effusion.

At admission the patient was found to be acutely ill and drowsy. The blood pressure was 130/90; pulse rate was 120 per minute; and temperature was 101° F. A fading petechial eruption was present on the trunk, and an erythematous, petechial eruption was seen on the face. Bilateral pleural effusion was noted. The left limbs were spastic and paralyzed. Some weakness of the right limbs also was present. A faint corneal haze was noted. The optic disks were elevated 1 to 2 diopters. Since the adjacent part of the retina was without the feathery edema of papilledema, elevation of the disks may have represented structural fullness. Retinopathy was not noted. Speech was dysarthric.

Pleural effusion and slight cardiac enlarge-

From the section of neurology, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota.
The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

ment were disclosed by a roentgenogram of the thorax. X-ray examination of the skull gave normal results. The value for hemoglobin was 13.4 gm. per 100 cc. of blood; for total proteins, 6.3 gm. per 100 cc. of serum, with an albumin-globulin ratio of 2.9:3.4. The sedimentation rate (Westergren) was 72 mm. in one hour; platelets numbered 101,000 per cubic millimeter of blood, and leukocytes, 4,200. Reaction of the Kahn test was negative. Urea amounted to 16 mg. per 100 cc. of blood. Urinalysis showed massive albuminuria and microhematuria. Sternal aspiration produced typical L. E. cells. Biopsy of specimens of the facial lesions revealed the microscopic picture of lupus erythematosus.

Comment on Case 1.—This girl had been intermittently ill for some years prior to the development of the typical pattern of lupus erythematosus. Sydenham's chorea and rheumatic fever had occurred four years and left hemiplegia six months before the appearance of the lesions on the skin. Thus, two major neurologic symptoms had been seen prior to the more typical signs of systemic disease. Other neurologic abnormalities such as dysarthria, drowsiness, and right hemiparesis were noted in addition to the characteristic cutaneous and visceral lesions of lupus erythematosus when the diagnosis was confirmed.

Case 2.—A 40 year old farmer was seen in June 1954 because of fatigue, generalized weakness, pain and swelling of the joints of the fingers and knees, and numbness and tingling in the lower extremities.

Between 1946 and 1951 he had lost 30 pounds for no apparent reason. Over several days in September 1951 numbness and weakness developed in the lower extremities. The numbness progressed to involve his body up to the nipples. Within a week he was paraplegic and had lost control of his bladder and bowels. He apparently had a mild fever and his neck was slightly stiff. Histamine, Chloromycetin, and penicillin were administered, but the use of penicillin was discontinued because of a generalized skin rash. Toward the end of his six weeks' hospitalization he began to improve, and a month later he was using a walker. Within six months he had returned to his farm work, complaining of only minimal weakness and hypesthesia in the lower limbs. Control of his bladder and bowels had also improved, although he continued to have urgency of urination and inability to retain a liquid stool.

In the summer of 1953 he was found to be anemic. Vitamin B_{12}, liver extract, and iron were prescribed. Later blood was administered. Tiredness, fatigue, exertional dyspnea, and episodes of swollen, painful fingers and knees and an additional loss of 30 pounds occurred, and he was referred for further examination. There had been no change in his neurologic status.

Physical examination disclosed a blood pressure of 124/90. A firm node was noted in the right axilla. Slight, nonpitting edema was present at both ankles. Cutaneous lesions were not seen and results of the general examination otherwise were normal. The patient's gait was slightly ataxic, and he was unable to hop well on either foot or to walk in tandem along a line. A suggestive Romberg sign was present. Minimal weakness was noted in the flexor muscles of the neck; there was slight generalized weakness in the lower limbs. The muscle-stretch reflexes were markedly exaggerated and bilaterally equal. Bilateral Babinski responses were elicited. Abdominal, cremasteric, and anal reflexes were absent. The tone of the anal sphincter was decreased. Vibratory sensibility was almost absent in the lower extremities; position sense of the toes was slightly diminished. Subjective disturbance for superficial sensations was present in the legs, and a patchy decrease could be demonstrated over the feet.

Roentgenograms of the head and thorax disclosed nothing abnormal. The value for hemoglobin was 11.4 gm. per 100 cc. of blood; erythrocytes numbered 3,790,000 per cubic millimeter of blood, and leukocytes, 3,800. The sedimentation rate was 75 mm. in one hour (Westergren); reaction of the Kline test was negative; the value for total proteins was 6.48 mg. per 100 cc. of serum; the albumin-globulin ratio was 3.67:2.81. Gastric analysis gave normal results. Urinalysis showed albuminuria, hyaline, and granular casts, microhematuria, a few leukocytes, and no Bence-Jones protein. The result of the L. E. clot test was positive. Sternal aspiration produced L. E. cells.

Comment on Case 2.—Almost three years prior to the establishment of the diagnosis of systemic lupus erythematosus, this patient had suffered an attack of myelitis. Even before the myelitis came on, his general health had not been good. Although the neurologic disturbance abated greatly, he was still left with some deficits. At that time he was noted to be sensitive to penicillin. He had continued to suffer from fatigue, which had become more pronounced a year before study when refractory anemia was noted. The history of joint pain and swelling, the elevated sedimentation rate, albuminuria, and microhematuria all were characteristic of systemic lupus erythematosus. The clot test and typical appearance of the marrow confirmed the diagnosis. In retrospect, this patient is seen to have had a long, progressive illness and the myelitis may well have been an early symptom of his systemic disease.

Case 3.—In January 1952 a 37 year old woman came to the clinic complaining of fatigue of a year's duration, as well as intermittent swelling of the left ankle. She had occasional backaches and a pin-and-needle sensation in her left arm. At times she had noticed some mottled cyanosis of the left leg when in a warm shower. She had had four miscarriages. Results of general physical, laboratory, and x-ray examinations were normal, except for slight swelling of the periarticular soft tissue of the left ankle.

In June 1952 she noted episodes of transient diplopia and dizziness, and consulted a neurologist in her home community. A diagnosis of multiple sclerosis was considered. These symptoms then cleared. In September 1952 she noticed heaviness of the head, with a feeling that there was movement inside her head. At times the vision of the left eye became foggy. Simultaneously, she also noticed numbness and tingling of the plantar aspect of the lateral four toes of the left foot. She soon improved, but in December 1952 episodes of vertigo and severe nausea developed and tinnitus in the left ear was noted. The paresthesias in the left toes spread to involve the whole left foot. Likewise, she noticed multiple transient joint pains as well as episodes of numbness and tingling of the tongue, legs, and arms.

When she was seen again in January 1953, results of general physical and neurologic examinations were normal. The leukocyte count was 3,200 per cubic millimeter of blood. The sedimentation rate was 50 mm. (Westergren) in one hour. Because of the history of joint pains, the low leukocyte count, and the elevated sedimentation rate, an L. E. clot test was done. The result was positive. The cerebrospinal fluid was normal except for a total protein content of 100 mg. per 100 cc. When she was discharged, it was uncertain whether the patient was suffering from lupus erythematosus or multiple sclerosis. However, during the next six weeks she again noted multiple transient joint pains, and an intermittent fever developed.

On readmission of this patient in March 1953, the result of an L. E. clot test was still positive. The leukocyte count was 3,800 per cubic millimeter of blood and the sedimentation rate was 77 mm. in one hour (Westergren). Her oral temperature was 102° F. The value for total serum proteins was 6.6 mg. per 100 cc. The albumin-globulin ratio was 3.9:2.7. Because of the course of the disease — swollen and painful joints, intermittent fever and evanescent neurologic complaints — and the laboratory findings of leukopenia, elevated sedimentation rate, and a positive result of the L. E. clot test — it seemed apparent that she was suffering from systemic lupus erythematosus.

The patient began to receive cortisone therapy in March 1953. The temperature promptly returned to normal. During the next month while she was receiving varying doses of cortisone, pain as well as muscle weakness developed in the right arm, and on examination a sensory loss was noted which appeared to be in the distribution of the eighth cervical nerve root or lower brachial plexus. Caloric studies revealed depression of the function of the left labyrinth. Only minimal loss of hearing was noted. Since that time her course has continued to be variable with transient episodes of diplopia, nystagmus, vertigo, and occasional fever.

Comment on Case 3.—This patient also had a gradual decline in health. Over the six month period prior to the diagnosis of lupus erythematosus, neurologic symptoms occurred which included episodes of diplopia and dizziness, decreased visual acuity, and numbness and tingling of several limbs. True vertigo later was experienced. In view of these scattered neurologic symptoms, the diagnosis of multiple sclerosis was considered. Later, after the diagnosis of lupus erythematosus had been made, neurologic abnormalities continued to develop. Definite neuropathy as well as symptoms of involvement of the brain stem or of cranial nerves was noted. Nystagmus and depression of the left labyrinthine responses were present.

DISCUSSION

It is now known that neurologic abnormalities often occur during the course of systemic lupus erythematosus. Neurologic symptoms or signs have been found in this generalized disease in about a fourth of patients.[1] Such an association certainly would appear to be more than a chance relationship. Generalized and focal convulsions, subarachnoid hemorrhage, aphasia, monoplegia, hemiplegia, quadriplegia, paraplegia, vertigo, nystagmus, neuropathy, choked optic disks, diplopia, cortical blindness, and disorders of movement may be seen as evidence of neurologic involvement in systemic lupus erythematosus. Psychiatric abnormalities also have been noted. They include emotional lability, severe anxiety, mental obscuration, depression, obsessive trends, paranoid reactions, and hallucinations.

Published studies on the neuropathology of systemic lupus erythematosus have been few, at least in part because of the extreme variability of the findings. Fibrinoid changes in the walls of small blood vessels, with associated proliferative reaction causing narrowing or occlusion and the resultant production of vascular insufficiency or infarcts, would appear to be one of the main pathologic features. Chance location of such vascular changes within the central nervous system could account for the varied manifestations.

Since systemic lupus erythematosus may be a chronic, smoldering affection, it is conceivable, as we have said at the outset of this paper, that symptoms referable to the central nervous system might occur well before other more characteristic manifestations of the illness. But this concept that neurologic abnormalities may be one of the first manifestations of systemic lupus erythematosus has received scant attention, possibly because of the difficulty in proving the relationship.

In their study on epilepsy and lupus erythematosus, Russell and his associates[2] commented that convulsive seizures occurring years before the other manifestations of lupus erythematosus may be the first symptom of the generalized disease. They also noted the intractability of these convulsions to the usual anticonvulsant therapy.

Bauer and his co-workers[3] reported a case similar to our case 1. In theirs, rheumatic fever and chorea occurred some nine months before a typical "butterfly rash." Their interest was mainly aroused by the rheumatic fever as an early symptom of lupus erythematosus, and they commented little on the chorea.

In all three cases presented here, evidence of neurologic dysfunction had ap-

peared prior to establishment of the diagnosis of systemic lupus erythematosus. These abnormalities included myelitis with paraplegia, choreiform movements and hemiplegia, and cranial and peripheral neuropathy. It is true that the absolute causal relationship cannot be established, but the likelihood of the relationship nevertheless strongly persists.

SUMMARY

Three cases of systemic lupus erythematosus are presented in which prominent neurologic abnormalities occurred prior to the establishment of the diagnosis of lupus erythematosus. It is suggested that neurologic signs or symptoms may be among the first manifestations of this generalized disease.

REFERENCES

1. Clark, E. C., and Bailey, A. A.: Neurologic and psychiatric findings in lupus erythematosus, Tr. Am. Neurologic A. In press.
2. Russell, P. W., Haserick, J. R., and Zucker, E. M.: Epilepsy in systemic lupus erythematosus; effect of cortisone and ACTH, Arch. Int. Med. 88:78, 1951.
3. Bauer, F. K., Riley, W. C., and Cohen, E. B.: Disseminated lupus erythematosus with Sydenham's chorea and rheumatic heart disease: Report of case with autopsy, Ann. Int. Med. 33:1042, 1950.

■ Before concluding these pages, it may be proper to observe once more, that an important object proposed to be obtained by them is, the leading of the attention of those who humanely employ anatomical examination in detecting the causes and nature of diseases, particularly to this malady. By their benevolent labours its real nature may be ascertained, and appropriate modes of relief, or even of cure, pointed out.

To such researches the healing art is already much indebted for the enlargement of its powers of lessening the evils of suffering humanity. Little is the public aware of the obligations it owes to those who, led by professional ardour, and the dictates of duty, have devoted themselves to these pursuits, under circumstances most unpleasant and forbidding. Every person of consideration and feeling, may judge of the advantages yielded by the philanthropic exertions of a Howard: but how few can estimate the benefits bestowed on mankind, by the labours of a Morgagni, Hunter, or Baillie.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

Prostigmine-Induced Muscle Weakness in Myasthenia Gravis Patients

Lewis P. Rowland, M.D., Marvin C. Korengold, M.D.
Israeli A. Jaffe, M.D., Leonard Berg, M.D.
and G. Milton Shy, M.D.

IN RECENT YEARS several authors have discussed a syndrome of muscular weakness in patients with myasthenia gravis which is attributed to overtreatment with anticholinesterase medication rather than to the disease itself.[1-6] Although there is suggestive evidence that OMPA [1,2] and TEPP[3] can actually produce weakness in myasthenic patients, the status of prostigmine in this regard is less certain. Because none of the newer preparations has supplanted prostigmine, it is most crucial to ascertain whether this drug can indeed cause weakness in myasthenia gravis patients.

There is evidence from animal experiments that excessive amounts of acetylcholine[7,8] or prostigmine[9,10] at the motor end-plate may cause neuromuscular block. Analagous experiments in humans have been inconclusive, however. Acetylcholine injected intraarterially has caused weakness in both normals[11] and myasthenics,[12] but when prostigmine itself has been given intraarterially, weakness has been produced only in normals[11] or in patients whose hands had not previously been clinically weak.[13]

Furthermore, there has been no convincing demonstration that weakness has actually been produced by prostigmine in clinical practice. In the one well-documented case[14] in which this seems to have been possible, the patient improved when the intravenous dose was reduced from 14 to 6 mg. per hour, but the crisis followed a thymectomy and may have been resolving spontaneously.

On the other hand, there is evidence that patients with myasthenia gravis have more tolerance for prostigmine than normals. Myasthenics are usually less likely than normals to experience muscarinic symptoms or fasciculation when given a test dose of prostigmine,[15] and many patients have been given large amounts of the drug in treatment without apparent deleterious effect. Whereas few patients require more than 500 mg. orally each day, some need as much

From the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.
Read at the sixth annual meeting of the American Academy of Neurology, Washington, D. C., April 29, 1954.

as 1,000 mg.[16] and there are unreported patients who have received 2,500 mg. daily. For patients in crisis, doses as high as 22 mg. an hour[17,18] have been given intravenously, but in patients already maximally weak it is not possible to evaluate accurately the adverse effects of a drug on muscle strength. Several authors state that the possibility of giving too much prostigmine to a patient in crisis is remote[19] and that there is greater likelihood of giving inadequate amounts when a patient is critically ill but not in a respirator.[17,20,21]

It is true that there are toxic effects of prostigmine other than weakness which may limit the amount given to any individual. Although usually controlled by small doses of atropine, the muscarinic effects of prostigmine – abdominal cramps, diarrhea, tracheobronchial secretion, and bronchospasm – may be severe[22] and have led some authors to advocate withdrawal of medication for patients being treated in a mechanical respirator.[5,6,23] Drug-induced weakness, however, is a more confusing symptom in a myasthenic patient and is potentially more dangerous than the others.

The problem would remain purely academic if all patients with myasthenia were rendered symptom-free by small amounts of the drug. There are patients who can perform their daily activities efficiently and who do not require large doses, but there are also many patients who are neither completely nor continuously free of symptoms. There are also some who improve initially but later seem to be refractory to the beneficial effects of the drug, and there are even some patients who seem to have myasthenia gravis but never respond to the drug in diagnostic fashion.[17,24] For any of these patients whose symptoms are incompletely controlled, the question arises whether increased amounts of prostigmine would be beneficial or dangerous. This decision is especially important in the management of patients in myasthenic crisis.

In an effort to determine whether myasthenic symptoms are reversible by maximally tolerated doses of prostigmine and whether large amounts of this drug can produce weakness in myasthenic patients, the following study was undertaken.

METHOD

Four patients with myasthenia gravis were studied. Each of them had a characteristic history and responded to prostigmine to some degree. Intravenous infusions of prostigmine methylsulfate were administered in gradually increasing amounts, starting with 1 mg. per hour; the concentration of the drug in normal saline was such that 100 cc. of fluid was usually given each hour. Although some patients received the infusions at a more accelerated rate for a short while, no patient received a total volume of more than 500 cc. in the course of an infusion lasting less than five hours.

Except where otherwise indicated, 0.1 mg. atropine sulfate was added to the solution for each 1 mg. prostigmine. This amount was usually sufficient to prevent the appearance of muscarinic symptoms, but supplemental doses of atropine were sometimes necessary. No patient received more than 2 mg. atropine during a single infusion of prostigmine.

Except for case 1, who could not tolerate more than three hours without medication, prostigmine was withheld

from each patient for at least 12 hours prior to an infusion.

During the infusions, grip strength was measured with a Collins spring hand dynamometer. Arm strength was measured by the number of times the arm could be alternately raised above the head and lowered to the side, and the number of seconds the arm could then be held at shoulder level. During most of these tests the patient remained sitting in a chair between test periods. During one infusion, when the patient was supine, the number of seconds the head could be elevated from the bed was recorded and the number of times the knee could be bent was counted. Other clinical observations were made when indicated.

During each experiment, resuscitation apparatus was immediately at hand and a physician experienced in endotracheal intubation was alerted to the possibility of untoward reaction.

PROTOCOLS

Case 1.—H. H., a 43 year old woman, had had generalized myasthenic symptoms for four years. For more than a year she had been confined to her home and spent most of her time in bed. Weakness of the extremities, face, jaws, tongue, and ocular muscles was marked but she had not had any major respiratory difficulty. She required assistance for the most fundamental activities and for a time alimentation could be achieved only by a nasogastric tube. She had never received more than 300 mg. of oral prostigmine daily and it was our opinion that she would improve if given more.

However, prostigmine in amounts as large as 4 mg. an hour given intravenously for three hours produced no improvement. On two other occasions when she received 10 mg. in 60 and 90 minutes, respectively, she seemed worse rather than better. She was so ill before the infusion was given that the change was difficult to measure, but extremity strength, speech, and ability to swallow all seemed to be even

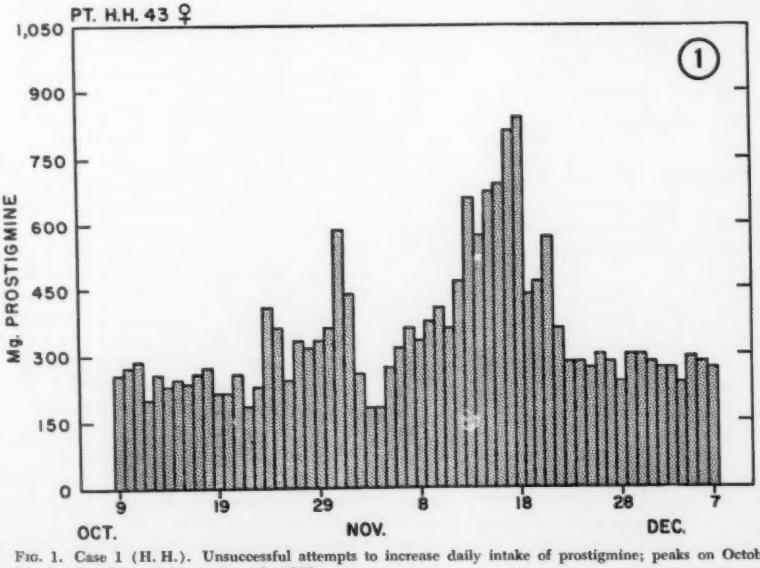


FIG. 1. Case 1 (H. H.). Unsuccessful attempts to increase daily intake of prostigmine; peaks on October 24, October 31, and November 18, 1953.

more seriously impaired. On another occasion she seemed worse after receiving 21 mg. in six hours (3 mg. an hour for three hours followed by 4 mg. an hour for three hours), and she said that her condition resembled the response she had had to quinine some years earlier. When given 10 mg. Tensilon (edrophonium chloride) intravenously at this point, she showed no response whatsoever.

It was thought that a more gradual increase in medication might provide benefit unattainable with infusions, but on three different occasions (figure 1) increases in oral medication up to 900 mg. a day failed to provide any increase in strength. The first trial was terminated because the patient seemed somewhat weaker and the second was terminated because other studies were being done. The third attempt was discontinued because she had an episode of severe anterior chest pain which was not accompanied by electrocardiographic changes and which improved slowly after the administration of atropine.

That she was not completely refractory to prostigmine became evident when she subsequently experienced a respiratory crisis and had to be treated in a mechanical tank respirator (Drinker-Collins). While receiving 24 mg. a day intramuscularly, she was extremely weak but she was able to write, gesture, and move her extremities to a limited degree. When prostigmine was completely withdrawn, she became virtually immobile. Five days later, when prostigmine therapy was reinstituted, her responsiveness was approximately the same as it had been. Since that time, several attempts to reduce the daily dose have been followed by increased weakness, but increased amounts of prostigmine parenterally have not been of significant benefit.

Case 2.—H. R., a 38 year old man, had myasthenia gravis for two years. His disease was manifest by ptosis of the left eyelid and weakness of both shoulder girdles, especially the left. Although he occasionally complained of diplopia, objective evidence of ocular muscle weakness was limited to transient nystagmus on lateral gaze. Other cranial nerve symptoms appeared from time to time and he had brief episodes of dyspnea which were never severe. General fatigue impaired his ability to work although he never had weakness of the hands or lower extremities.

When he was tested at appropriate intervals but given no medication (figure 2), there was no appreciable fatigue.

On one occasion he was given an infusion which did not contain atropine. After receiving 1.5 mg. prostigmine in 30 minutes, he experienced rhinorrhea, lacrimation, abdominal cramps, and emesis. Fasciculation was generalized and prominent. However, his arm strength seemed to improve at this time (figure 3). The muscarinic symptoms subsided rapidly when he was given atropine intravenously.

Atropine was included in the infusion on another occasion (figure 4) and arm strength improved initially. When he had received a total of 10 mg. prostigmine in 2¾ hours, his arms became weaker and grip strength, usually not affected at all, declined precipitously. Cranial nerve function was essentially unchanged. When the infusion was discontinued, he rapidly regained strength in all actions tested.

Case 3.—D. W., a 44 year old man, had myasthenia of eight months' duration, confined to the extraocular muscles and eyelids. The control tests without medication showed no significant fatigue of arm strength or grip (figure 2).

When he was given the infusion illustrated in figure 5, his arm strength seemed to decline at first and then showed wide variations, while grip strength remained unaffected. By the end of two hours there was no striking change in arm strength, but ptosis and ocular mobility improved. The rate of infusion was accelerated, and although there was a downward trend there was no definite change until he had received a total of 8 mg. in 2¾ hours. He then suddenly complained that he could hardly move his arms or legs and could not hold his head erect. Ocular function was notably worse. Grip strength had declined to values of 60 and 36 pounds from control levels of 110 and 96. He was able to raise his arm overhead only 17 times in contrast to 96 and he could hold his arm at shoulder level for only 3 seconds in contrast to 90. This weakness occurred in the complete absence of muscarinic symptoms, which had been blocked by atropine, and there were no fasciculations. Once again recovery was rapid when the infusion was discontinued.

Because it was not clear whether this weakness resulted from the total amount of prostig-

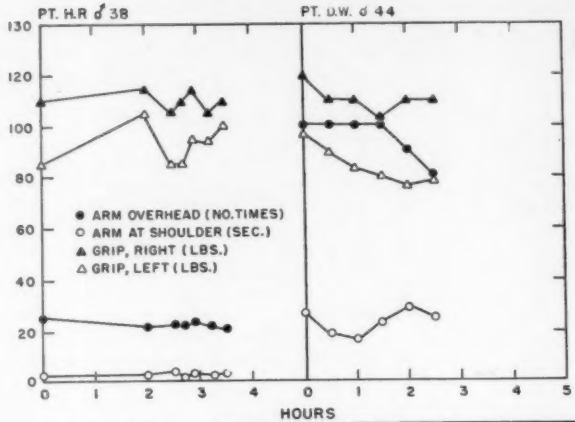


FIG. 2. Cases 2 (H. R.) and 3 (D. W.). Control tests of strength; no medication given. Lack of pronounced fatigue effect.

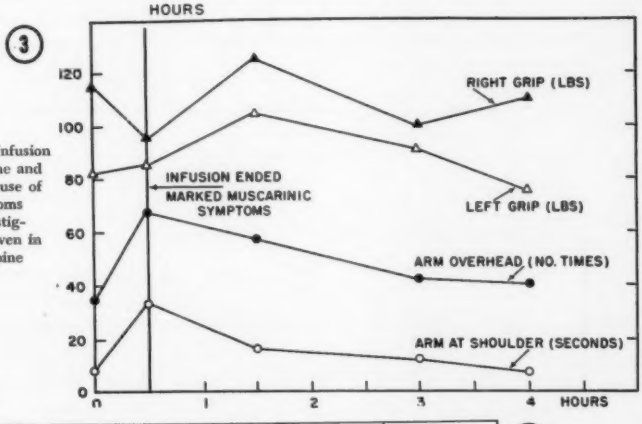


FIG. 3. Case 2. Infusion started at zero time and discontinued because of muscarinic symptoms after 1.5 mg. prostigmine had been given in 30 minutes (atropine omitted).

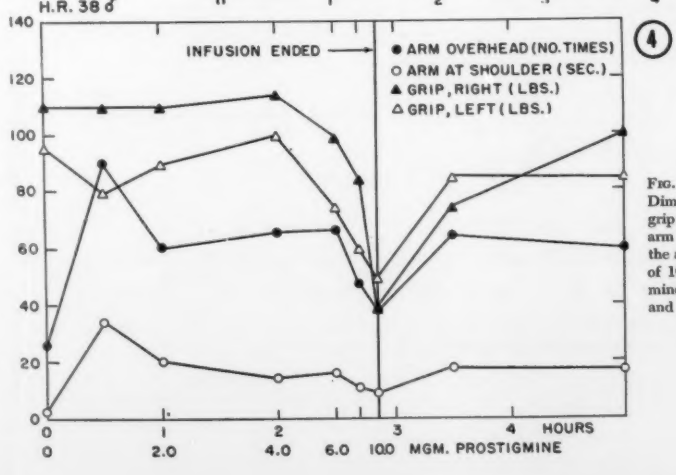


FIG. 4. Case 2. Diminution in grip strength and arm strength after the administration of 10 mg. prostigmine in two hours and 30 minutes.

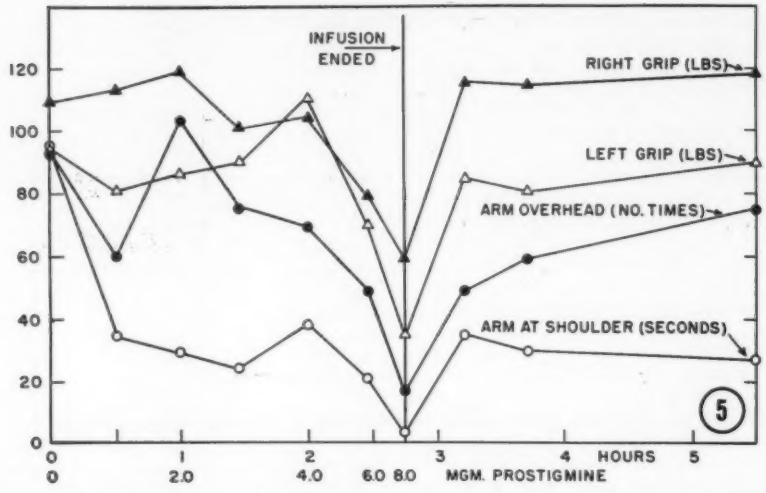


FIG. 5. Case 3. Diminution in grip strength and arm strength after the administration of 8 mg. prostigmine in 2¾ hours.

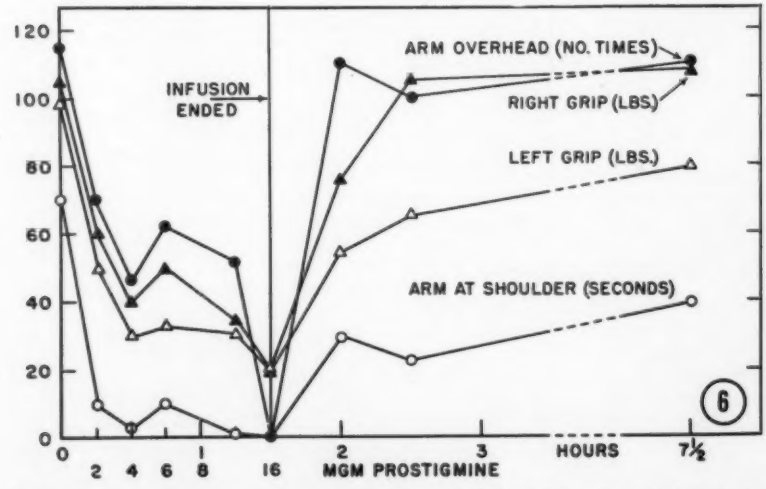


FIG. 6. Case 3. Diminution in grip strength and arm strength during infusion of prostigmine started at rate of 8 mg. per hour; rate doubled during last 30 minute period.

mine administered or whether it was related to the rapid rate of infusion during the last 15 minutes, another infusion was started at the latter rate (8 mg./hour). This time (figure 6) there was a rapid decline in all functions recorded on the graph, but again ocular function improved initially. After the first hour the infusion was accelerated and he received a total of 16 mg. in 90 minutes. Weakness became profound. Ptosis and ophthalmoplegia were worse than prior to the infusion. Dysarthria, dysphagia, and facial weakness were apparent, and he required assistance in sitting and standing. Fasciculation was observed in several muscles but he had no muscarinic symptoms. There was no change in the electrocardiogram. When the infusion was discontinued, he regained strength rapidly.

During the latter infusion he received a total of 2 mg. of atropine, including 0.4 mg. given at the end of 30 minutes because of abdominal cramps. On another occasion he received an infusion which contained an equal amount of atropine but no prostigmine. At the end of 90 minutes he was given an additional 0.8 mg. This total of 2.8 mg. atropine had no discernible effect other than to cause mild dryness of the mouth; there was no appreciable change in arm strength or ocular muscle function.

Case 4.—L. C., a 23 year old woman, had continuing symptoms of myasthenia, despite a thymectomy three years earlier. At the time of examination weakness was confined to the extremities, but was severe enough to incapacitate her partially. She could care for herself and do some housework but she was not able to be gainfully employed.

When medication was withheld for 12 hours, the weakness of her extremities increased significantly and was reversed, although incompletely, by infusions of prostigmine. At rates up to 4 mg. an hour for three hours she showed no adverse effects.

During the infusion started at 5 mg. per hour (figure 7), she improved initially. Although there was some decline in performance at 2½ hours, this was not prominent. During the last 30 minutes the rate was more rapid, and she received a total of 20 mg. in 3½ hours. At the time the infusion was discontinued she still had shown no striking change, but 30 minutes later she was noted to be extremely weak. Ptosis, facial weakness, and dysarthria were observed for the first time, in addition to marked weakness of the extremities and neck. Her vital capacity had not changed and there was no ocular muscle weakness. She complained of marked malaise, but no specific muscarinic symptoms occurred and fasciculation was not

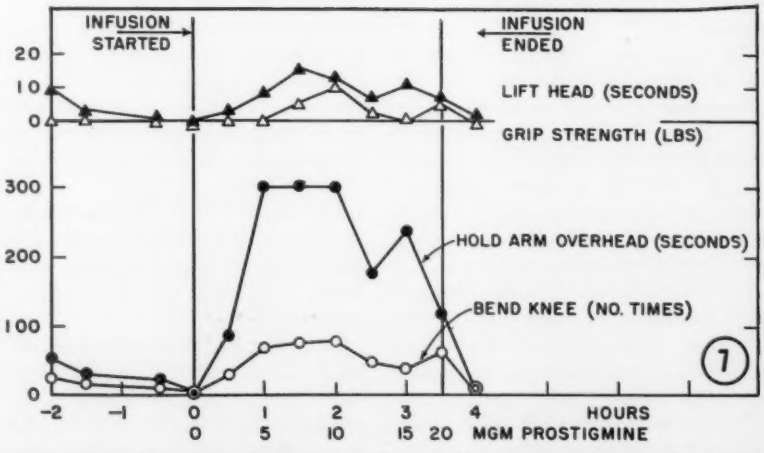


FIG. 7. Case 4 (L. C.). Increased weakness in muscles of neck, hands, arms, and legs; reaction delayed until after infusion had been discontinued.

seen. Formal testing was not repeated because of the patient's discomfort, but the cranial nerve signs rapidly disappeared and some strength returned to the extremities within 30 minutes.

DISCUSSION

The weakness produced in these experiments was very suggestive in the first patient, unequivocal in the second, and profound in the last two. This weakness was so striking that great caution will have to be exercised in any future attempt to elucidate the mechanism of this phenomenon. The limited data at hand permit some deductions.

The control tests without medication indicate that the rest periods were adequate and that repetition of muscle testing per se did not cause fatigue. This is also indicated by the rapid return of strength in each case after the infusion was discontinued. The failure of 2.8 mg. of atropine to have any effect on muscle strength when given to case 3 indicates that the weakness observed in the other experiments was certainly not due to atropine, but is to be attributed to prostigmine.

The improvement in arm strength in case 2 (figure 2) at the time he was experiencing a severe muscarinic reaction indicates that these toxic symptoms are not necessarily followed by aggravation of weakness in some nonspecific fashion, as is sometimes seen in these patients during the course of a respiratory infection or some other stress.

In a composite graph of the infusions which produced weakness in less than four hours (figure 8), there is a suggestion that the smallest amount of prostigmine required to produce weakness is less for patients with mild forms of the disease than for those whose disease is severe. Nevertheless, it must be emphasized that no definite conclusions may be made regarding the "threshold" rate of prostigmine administration which produces weakness. The number of patients in this series is too small, the rate of infusion was often changed in the course of a single experiment, and there are no data relating to variability of response from day to day.

The pattern of change during the infusions was not consistent from patient to patient. Case 2 and case 4 both showed improvement of clinically affected muscles before prostigmine-induced weakness appeared, but case 1 showed no improvement whatsoever. In case 3 the paradoxical observation was made that the muscles of one eye improved while the other became worse. In addition, muscles which were weak before the infusion seemed to get weaker simultaneously with muscles which had not previously been involved. Fasciculation was present in two patients at the time of weakness but was absent in the other two. In case 3 fasciculation was observed at the time of weakness during one infusion but not in the other. In case 2 fasciculation could be evoked almost immediately by increasing the rate of infusion and abolished with equal rapidity by slowing the infusion. The speed with which these changes occurred and the rapid improvement in each case provide confirmatory evidence that, at rapid rates of infusion, mechanisms for the disposal of prostigmine are also rapid.[27] The delayed reaction in case 4 is a possible exception.

The theoretical implications of this study are not clear. Churchill-Davidson and Richardson[26] have suggested that the pathophysiologic basis of myasthenia gravis is an alteration of the end-plate so that the normal depolarizing action

of acetylcholine is converted into activity resembling curare-like inhibition. This theory is based upon the observation that decamethonium, which theoretically resembles acetylcholine in its activity and behaves like a depolarizing agent in normals, ultimately behaves like a competitive inhibitor when given to patients with myasthenia.

It is not possible to state definitely whether or not the data we have obtained support or contradict this theory. Whether prostigmine acts primarily through inactivation of cholinesterase by maintaining a high concentration of acetylcholine at the end-plate[27] or whether it has a direct action on the end-plate,[28] the mechanism of prostigmine block in normals ought to have the characteristics enumerated for depolarization. In myasthenics, according to the theory of Churchill-Davidson and Richardson, it should behave like a competitive inhibitor. These authors list three characteristics as differentiating one type of block from the other.

First, depolarization block is enhanced by prostigmine and Tensilon (edrophonium chloride), whereas block by competition is reversed by these drugs. When, as in our experiments, the block is produced by prostigmine, the effect of additional amounts of the same drug cannot be used as a differential criterion. Tensilon was given to only one of our patients at the time of weakness and it had no observable effect whatsoever. We did not administer it to the others because of the dramatic changes which had already occurred. Osserman and

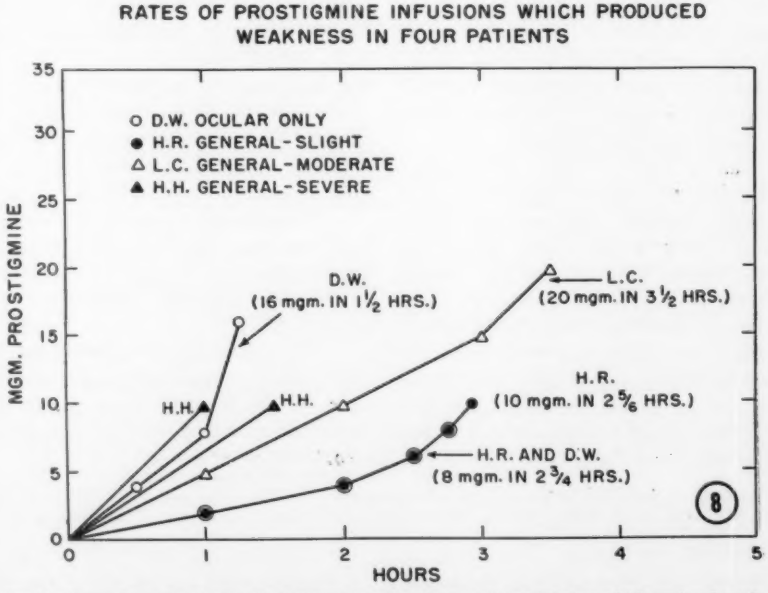


FIG. 8. Composite graph of rates of administration of prostigmine during infusions which produced weakness in four patients. Note that patients D. W. and H. R. became weak at lower rates than L. C. or H. H.

Kaplan[4] have reported that Tensilon aggravates weakness in patients who are receiving too much prostigmine.

Second, fasciculation is said to occur in block by depolarization but not in block by competitive inhibition. As indicated above, prostigmine-induced weakness was not consistently associated with fasciculation, although it did occur twice.

The third criterion listed by Churchill-Davidson and Richardson is the difference in response to single and tetanic nerve stimuli in the two types of block. We do not have information relative to this point.

Additional data must therefore be accumulated before any definitive statement may be made regarding the mechanism whereby prostigmine produces weakness. We have not adopted the term "cholinergic crisis"[1,4] because this implies more knowledge than we possess; it is possible that this phenomenon is due to a direct cellular effect of the drug in toxic amounts, without regard for the acetylcholine system.

In any event, the clinical conclusions to be derived from this study leave the original problems only partially elucidated. That prostigmine can cause weakness seems unequivocal, but the amounts utilized in these infusions are not likely to be equalled by oral administration. Furthermore, if it is correct that the more severe the disease the greater the tolerance for prostigmine, then it is still appropriate to give large amounts to patients who are seriously ill. However, it must be recognized that in some patients the benefits to be derived from prostigmine are extremely limited and that additional amounts may not only fail to produce improvement, but may actually be dangerous.

SUMMARY

1. Prostigmine administered in large amounts intravenously has been demonstrated to cause significant weakness in patients with myasthenia gravis.

2. Prostigmine-induced weakness was usually preceded by improvement in clinically weak muscles but the improvement was usually incomplete and in one patient large amounts of the drug failed to evoke any improvement before eliciting weakness.

3. There was no consistent pattern of weakness, but muscles which had not been clinically weak previously were usually affected simultaneously with "myasthenic" muscles.

4. Muscarinic symptoms were not present at the time of weakness when atropine was administered with the prostigmine; fasciculation was present in some patients but not in others.

5. Recovery after prostigmine-induced weakness was rapid, confirming earlier observations that at rapid rates of administration disposal mechanisms are also rapid.

6. There is suggestive, but inconclusive, evidence that weakness was produced at slower rates of infusion in patients whose disease is mild than in those whose disease is severe.

The authors are indebted to the patients who cooperated in this study and to Drs. T. P. Fitch, G. D. Gammon, G. H. Marts, J. T. McHenry, and J. P. Williams who referred the patients to us.

REFERENCES

1. Wilson, C. W., Williams, J. P., and Miller, D. H.: The hazard of cholinergic crisis during treatment of myasthenia gravis with octamethyl pyrophosphoramide, Ann. Int. Med. 37:574, 1952.
2. Schulman, S., Rider, J. A., and Richter, R. B.: Use of octamethyl pyrophosphoramide in the treat-

ment of myasthenia gravis. Further observations, J.A.M.A. 152:1707, 1953.
3. Grob, D., and Harvey, A. M.: Observations on the effects of tetraethyl pyrophosphate (TEPP) in man, and on its use in the treatment of myasthenia gravis, Bull. Johns Hopkins Hosp. 84:532, 1949.
4. Osserman, K. E., and Kaplan, L. I.: Studies in myasthenia gravis. Use of edrophonium chloride (Tensilon) in differentiating myasthenic from cholinergic weakness, Arch. Neurol. & Psychiat. 70: 385, 1953.
5. Randt, C. T.: Myasthenia gravis, M. Clin. North America 37:535, 1953.
6. Hoefer, P. F. A., Aranow, H., Jr., and Rowland, L. P.: Therapy of myasthenia gravis, Neurology 3:691, 1953.
7. Briscoe, G.: The antagonism between curarine and acetylcholine, J. Physiol. 87:425, 1936.
8. Burns, B. D., and Paton, W. D. M.: Depolarization of the motor end-plate by decamethonium and acetylcholine, J. Physiol. 115:41, 1951.
9. Briscoe, G.: Depressant effect of prostigmin and its temporary antagonism by curarine, J. Physiol. 86:1P, 1936.
10. Briscoe, G.: The antagonism between curarine and prostigmin and its relation to the myasthenia problem, Lancet 1:469, 1936.
11. Harvey, A. M., Lilienthal, J. L., Jr., and Talbot, S. A.: The effects of the intra-arterial injection of acetylcholine and prostigmine in normal man, Bull. Johns Hopkins Hosp. 49:529, 1941.
12. Wilson, A., and Stoner, H. B.: The effect of the injection of acetylcholine into the brachial artery of normal subjects and patients with myasthenia gravis, Quart. J. Med. 16:237, 1947.
13. Hutchinson, E. C., and Matthews, W. B.: The intra-arterial injection of neostigmine as a diagnostic test in myasthenia gravis, J. Neurol., Neurosurg. & Psychiat. 16:47, 1953.
14. Rider, J. A., Pickett, W. H., and Harrison, A. W.: Myasthenia gravis: Report of case receiving unusual dosage of neostigmine, Ann. Int. Med. 35: 463, 1951.
15. Viets, H. R.: Diagnosis of myasthenia gravis in patients with dysphagia, J.A.M.A. 134:987, 1947.
16. Eaton, L., M.: Care of the patient who has myasthenia gravis, M. Clin. North America 29:907, 1947.
17. Rowland, L. P.: Fatalities in myasthenia gravis, Tr. Am. Neurol. A. 78:158, 1953.
18. Gammon, G. D.: Discussion of reference 17.
19. Harvey, A. M.: Myasthenia gravis. In "Current Therapy," H. F. Conn (ed.), W. B. Saunders and Co., Philadelphia, 1954.
20. Viets, H. R.: Myasthenia gravis treated with large doses of neostigmine methylsulfate intramuscularly and intravenously, and with neostigmine bromide orally, Am. J. M. Sc. 208:701, 1944.
21. Viets, H. R.: Emergency treatment of myasthenia gravis, M. Clin. North America 10:1035, 1946.
22. Viets, H. R.: Myasthenia gravis. In "Current Therapy," H. F. Conn (ed.), W. B. Saunders and Co., Philadelphia, 1954.
23. Korey, S. R., and Randt, C. T.: Treatment of myasthenic crisis, J. Nerv. & Ment. Dis. 112:445, 1950.
24. Walsh, F. B.: Myasthenia gravis: Diagnosis and treatment, Rocky Mountain M. J. 49:757, 1952.
25. Goldstein, A., Krayer, O., Root, M. A., Acheson, G. H., and Doherty, M. E.: Plasma neostigmine levels and cholinesterase inhibition in dogs and myasthenic patients, J. Pharmacol. & Exper. Therap. 96:56, 1949.
26. Churchill-Davidson, H. C., and Richardson, A. T.: Neuromuscular transmission in myasthenia gravis, J. Physiol. 122:252, 1953.
27. Koelle, G. B., and Gilman, A.: Anticholinesterase drugs, Pharmac. Rev. 1:166, 1949.
28. Riker, W. F., and Wescoe, W. C.: The direct action of prostigmine on skeletal muscle; its relationship to the choline esters, J. Pharmacol. & Exper. Therap. 88:58, 1946.

Dr. Rowland's present address is the Division of Neurology, Montefiore Hospital, New York City.

■ Whilst conjecturing as to the cause of this disease, the following collected observations on the effects of injury to the medulla spinalis, by Sir Everard Home, become particularly deserving of attention. It thence appears, that none of the characteristic symptoms of this malady are produced by compression, laceration, or complete division of the medulla spinalis.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

Cerebral Metabolism of Glutamic Acid in Multiple Sclerosis

John E. Adams, M.D., Harold A. Harper, Ph.D.,
Gilbert S. Gordan, M.D., Ph.D., Maxine Hutchin, A.B.
and Richard C. Bentinck, M.D.

CURRENT STUDIES concerning the pathogenesis of multiple sclerosis are increasingly being directed toward altered metabolic processes. The present investigation deals with cerebral metabolism in multiple sclerosis, and particularly with the metabolism of glutamic acid and its amide glutamine in patients suffering from varying stages of the disease.

There is now available a suitable method for measuring the rate of cerebral blood flow (CBF) that permits a computation of the rate of utilization or liberation by the brain of any substance that can be accurately analyzed in blood.[1] By means of this technic, the rates of CBF and the cerebral metabolic rates (CMR) for oxygen, carbon dioxide, glucose, lactic acid, pyruvic acid, as well as for glutamic acid and its amide glutamine have been measured in patients with multiple sclerosis and in a series of normal control subjects.

A total of 32 patients with multiple sclerosis have been studied. The patients for the most part were admitted to the University of California Hospital, where a complete investigation of their clinical status was made and where they were independently examined by several members of the departments of neurology and neurosurgery.

No patient was included in the study unless the clinical findings and subsequent course established the diagnosis of multiple sclerosis. The patients were divided into three groups:

1. Those in an acute active exacerbation of the disease, or patients in an initial attack who subsequently were shown to have multiple sclerosis.

2. Those with advanced multiple sclerosis who, at the time of the study, evinced no signs of active progression of the disease. The disease in this stage has been termed "indolent multiple sclerosis."

3. Those who were either improving from an active exacerbation or recovering from an initial attack of the disease.

The average age of the patients with multiple sclerosis was 31 years (range

From the Cerebral Metabolic Research Laboratory of The Langley Porter Clinic of the State Department of Mental Hygiene, the Metabolic Research Facility, U. S. Naval Hospital, Oakland, and the departments of neurosurgery, surgery, and medicine, University of California School of Medicine, San Francisco.

Aided by grants from the Multiple Sclerosis Society and from Ciba Pharmaceutical Products, Inc., Summit, N. J.

22 to 59 years). The average duration of the disease for the entire group was 1.6 years.

Nineteen normal subjects were studied in the same fashion. The average age of the control group was 29 years, and therefore comparable to patients with multiple sclerosis.

METHOD

At the time of the study, the subjects were in a fasting state and had received no medication for 24 hours or longer. Needles were inserted into the jugular bulb and the femoral artery and connected to heparinized manifolds, as described in the original method of Kety and Schmidt.[1] In order to avoid the effects of emotional stimuli, as stressed by Scheinberg and Stead,[2] no further procedures were undertaken until the cardiac rate and arterial blood pressure were stable. Mean arterial blood pressures were continually measured by means of an air-damped mercury manometer. When a steady state was achieved an initial control study was then made, in which samples of arterial and mixed cerebral venous blood were drawn simultaneously at zero to one minute, and at 3, 5, and 10 minutes while the subject breathed a mixture of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen. Following the control study, 20 minutes were allowed to elapse in order to permit expiration of nitrous oxide, and at this point, a second blood bank for nitrous oxide was obtained in each case. During the 20-minute interval, 20 ml. of a 30 per cent solution of sodium succinate (6.0 gm.) was slowly administered into the internal jugular vein via the venous manifold.

In the early phase of the investigation, it was noted that the arterial blood pressure dropped profoundly during intravenous administration of sodium succinate. The drop was accompanied by nausea, sweating, and discomfort to the patient; it also cast doubt upon the accuracy of the second CBF determination because of the severe alteration in cardiovascular dynamics. Experiments in dogs showed that this drop in blood pressure after the intravenous administration of sodium succinate could be abolished by preliminary division of the vagus nerves. Thereafter, 0.5 mg. of atropine sulfate was given intravenously immediately prior to the first determination of CBF in all patients who received sodium succinate. This effectively prevented the drop in blood pressure in all but one patient. At completion of administration of sodium succinate, which was timed to coincide with the end of the 20-minute expiration period, a second CBF determination was made.

With each CBF determination, "metabolic samples" of arterial and cerebral venous blood were taken simultaneously —10 ml. immediately before the first CBF sample and an additional 10 ml. drawn into the same syringe directly following the 5-minute CBF specimen. Part of the specimen was then placed in a fluoride tube for determination of the glucose and lactate content. In seven patients and 11 normal subjects, separate specimens were drawn for determination of pyruvic acid content and were immediately dispersed into trichloracetic acid.

Blood oxygen and carbon dioxide analyses were made in duplicate by the manometric technic of Van Slyke and Neill,[3] as modified by Kety and Schmidt.[4] Glucose was determined by the colori-

metric method of Nelson[5] as well as by the original iodimetric titration technic of Somogyi.[6] Glutamic acid and glutamine were measured by the microbiologic method of Harper,[7] utilizing *Lactobacillus arabinosus*. Pyruvic acid was measured by a modification of the procedure of Friedemann and Haugen,[8] and lactic acid by a modification of the method of Miller and Muntz.[9] CBF and CMR's were calculated by the formula of Kety and Schmidt.[1] All of the values are expressed as ml. or mg. per 100 gm. of brain per minute, with the single exception that we have chosen to express the values for glutamic acid and glutamine as the observed arteriovenous differences rather than as the calculated CMR. This value permits inclusion of several cases where determination of CBF was faulty and avoids multiplication of technical and mathematical errors. Since the rate of CBF of our patients with multiple sclerosis did not differ from that of normal subjects, the use of arteriovenous differences for glutamic acid and glutamine seems to us more accurate than the use of cerebral metabolic rates.

RESULTS

In the control series, 16 of the 19 normal subjects showed a definite uptake of glutamic acid by the brain (table 1). (The sensitivity and accuracy of the method of assay for glutamic acid and glutamine are such that a difference of more than 0.2 mg. per 100 ml. is required to be significant. Uptake or utilization is indicated by a positive arteriovenous difference, that is, when the arterial value exceeds the venous value. Similarly, a negative arteriovenous value signifies release or liberation.) Of the

TABLE 1
CEREBRAL METABOLISM OF GLUTAMIC ACID AND GLUTAMINE—NORMAL SUBJECTS

	A-V mg./100 ml. before Succinate			A-V mg./100 ml. after Succinate		
Subject	Glutamic acid	Glutamine	Reaction	Glutamic acid	Glutamine	Reaction
C	+3.4	−4.0	Amidation			
S	+1.8	−2.4	Amidation			
L'	+1.8	−1.8	Amidation			
M	+0.8	−0.4	Amidation			
P	+0.2	−1.2	Amidation			
B	+0.6	−1.2	Amidation			
L	+0.4	−0.6	Amidation			
GG	+0.2	−1.6	Amidation	+0.2	−0.7	Amidation
JJ	+0.5	−0.5	Amidation	−0.4	+0.4	De-amidation
CA	+2.4	−2.8	Amidation			
SM	+0.5	−1.6	Amidation			
PE	+0.3	−1.8	Amidation			
JS	+0.7	−1.3	Amidation	+0.2	+0.4	Utilizes both
OH	+0.3	−0.3	Amidation	−0.6	−0.1	Liberates glutamic acid
MM'	+0.5	−2.1	Amidation	−0.1	+0.6	Utilizes glutamine
L''	−0.2	−0.2	Liberates both			
E	−0.7	−0.1	Liberates glutamic acid	−0.3	−0.6	Liberates both
JV	−0.1	−0.4	Liberates glutamine	+0.2	−0.2	Amidation
WI	+0.4	+0.2	Utilizes both			
Mean	+0.78	−1.26		−0.11	−0.02	

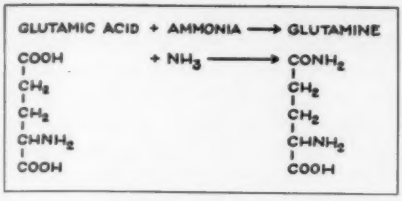


FIG. 1. Amidation of glutamic acid.

16 normal subjects who took up glutamic acid, 15 liberated glutamine into the cerebral venous blood. Since the CBF is 53 ml./100 gm. of brain/min., the average CMR of glutamic acid for the control group is +0.4 mg./100 gm. of brain/min. and is approximately balanced by the release of glutamine at a rate of −0.6 mg./100 gm. of brain/min. (table 1). For purposes of description, we have termed this process "amidation of glutamic acid" (figure 1). Of the four subjects who did not show distinct amidation, two (L" and JV) demonstrated values within the experimental error. One subject, E, definitely released glutamic acid from the brain, while subject WI demonstrated uptake of glutamic acid and probably of glutamine.

In 14 of 16 patients with active multiple sclerosis (table 2), amidation was clearly absent. One patient showed definite evidence of amidation (FB), and one (SM) showed only equivocal release of glutamine. The mean values for the arteriovenous differences of glutamic acid and glutamine were −0.28 mg. per 100 ml. and +0.43 mg. per 100 ml. respectively, a reverse of the pattern in normal subjects. Of the four patients who were recovering from the acute stage of the disease (table 3) and who were showing clinical signs of improvement, one showed positive evidence of amidation (CM). In another patient (MT), the arteriovenous differences were not sufficiently great to fall outside the experimental error. In patients with indolent or long-standing multiple sclero-

TABLE 2

CEREBRAL METABOLISM OF GLUTAMIC ACID AND GLUTAMINE—ACTIVE MULTIPLE SCLEROSIS

	A-V mg./100 ml. before Succinate			*A-V mg./100 ml. after Succinate*		
Subject	*Glutamic acid*	*Glutamine*	*Reaction*	*Glutamic acid*	*Glutamine*	*Reaction*
CL	−0.4	+2.4	De-amidation	+0.9	+0.4	Utilizes both
MK	−1.0	+2.6	De-amidation	−0.7	−1.2	Liberates both
WR	−0.1	+0.4	De-amidation	+1.2	−1.6	Amidation
JS	−0.1	+0.2	De-amidation	+0.4	−0.5	Amidation
JC	−1.2	+0.6	De-amidation	−0.2	+0.2	De-amidation
Gud.	−0.2	+0.8	De-amidation	−0.6	+1.1	De-amidation
MO	−0.2	+0.2	De-amidation	+2.1	−0.7	Amidation
Nun.	−2.1	+0.2	De-amidation	+0.8	+0.2	Utilizes both
JH	−0.2	−0.7	Liberates both	0	0	No turnover
JG	−0.5	−1.0	Liberates both	+0.6	0	Utilizes glutamic acid
NMc	+0.5	+0.3	Utilizes both	+0.3	−1.1	Amidation
CG	+0.4	+1.0	Utilizes both	+0.5	+0.5	Utilizes both
SM	0	−0.2	Liberates glutamine	−0.3	0	Liberates glutamic acid
CL	0	+1.4	Utilizes glutamine	+0.9	−0.9	Amidation
EG	0	0	No turnover	+0.1	−0.1	Amidation
FB	+0.7	−1.3	Amidation	−1.0	−0.3	Liberates both
Mean	−0.28	+0.43		+0.31	−0.5	

TABLE 3
CEREBRAL METABOLISM OF GLUTAMIC ACID AND GLUTAMINE
PATIENTS RECOVERING FROM ACUTE DISEASE

Subject	A-V mg./100 ml. before Succinate		Reaction	A-V mg./100 ml. after Succinate		Reaction
	Glutamic acid	Glutamine		Glutamic acid	Glutamine	
CM	+0.7	−0.2	Amidation	−0.3	+0.3	De-amidation
MT	+0.1	−0.1	Amidation ?			
MN	+1.1	+2.5	Utilizes both	+0.5	+0.5	Utilizes both
MR	+0.5	+0.9	Utilizes both	+0.4	+0.3	Utilizes both
Mean	+0.6	+0.7		+0.3	+0.4	

sis (table 4), only two of 12 patients showed evidence of amidation (BL, JO).

In order to determine whether the metabolic sample, half of which was taken immediately before the first CBF sample and half directly after the 5-minute CBF sample, accurately reflected the metabolic picture during the entire 10 minutes of each study, the values for glutamic acid and glutamine content in each CBF sample were compared with those of the "metabolic sample" in one patient (figure 2). In this figure, the values for the individual samples are superimposed over those of the metabolic sample (hatched areas). The good correlation between data derived from these two sampling technics permits use of the integrated metabolic sample instead of the numerous individual determinations.

In table 5 data are tabulated for CBF and CMR for oxygen derived from 218 determinations of CBF in 109 human subjects. It will be noted that the rates in multiple sclerosis are identical with those found in normal subjects of all ages from 13 to 76, and in patients with cerebral thrombosis or with schizophrenia. Our data are at variance with those of Tucker, Donald, and Farmer,[10] who report a decrease of CBF in certain cases of multiple sclerosis.

Following the administration of so-

TABLE 4
CEREBRAL METABOLISM OF GLUTAMIC ACID AND GLUTAMINE
INDOLENT MULTIPLE SCLEROSIS

Subject	A-V mg./100 ml. before Succinate		Reaction	A-V mg./100 ml. after Succinate		Reaction
	Glutamic acid	Glutamine		Glutamic acid	Glutamine	
JO	+0.2	−0.2	Amidation ?	−1.0	−0.3	Liberates both
BL	+0.2	−0.5	Amidation	−0.7	+0.3	De-amidation
EMc	+0.2	0	Utilizes glutamic acid	−0.2	−0.6	Liberates both
CK	0	+1.2	Utilizes glutamine	0	+0.6	Utilizes glutamine
VH	+0.8	+0.6	Utilizes both	+0.2	+0.3	Utilizes both
BA	+1.4	+1.3	Utilizes both	+0.6	+1.3	Utilizes both
LD	+1.2	+0.6	Utilizes both	−0.9	−0.7	Liberates both
NG	+0.6	+0.3	Utilizes both			
AK	0	−0.2	Liberates glutamine	0	−0.1	Liberates glutamine ?
EB	−2.1	−3.0	Liberates both	+0.5	+2.4	Utilizes both
KF	0	+1.6	Utilizes glutamine	+0.3	−0.7	Amidation
Thal.	−0.3	+0.7	De-amidation	−0.2	+0.4	De-amidation
Mean	+0.18	+0.20		−0.12	+0.24	

dium succinate to patients with active disease, an alteration in the cerebral metabolism of glutamic acid and glutamine occurred (table 2), so that the mean values for glutamic acid changed from a negative arteriovenous value of 0.28 mg. per 100 ml. to a positive value of 0.31 mg. per 100 ml., indicating a shift from release to uptake of glutamic acid by the brain. A converse reversal from uptake to release occurred with glutamine. No consistent response, however, was seen in individual cases of multiple sclerosis after the administration of sodium succinate, regardless of the stage of the disease, nor was there any consistent response in normal human subjects. As noted in table 6, there was also no significant alteration in CBF rates or in the CMR for oxygen, carbon dioxide, glucose, pyruvic acid, or lactic acid.

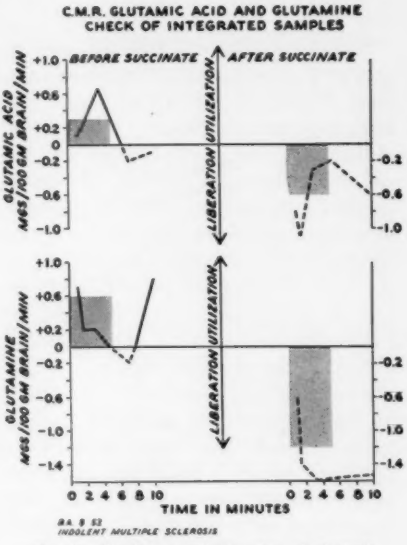


FIG. 2. Cerebral metabolic rates of glutamic acid and glutamine.

TABLE 5

Number of Cases	*Subjects*	*CBF Ml./100 gm. Brain/Min.*	*CMR O_2 Ml./100 gm. Brain/Min.*
23	Normals, age 13 to 39	52 ± 5	3.1 ± 0.2
30	Normals, age 40 to 70	47 ± 2	3.1 ± 0.2
6	Cerebrovascular accidents, age 29 to 38	49 ± 4	2.9 ± 0.4
12	Cerebrovascular accidents, age 40 to 59	49 ± 3	3.5 ± 0.3
16	Schizophrenia, age 15 to 37	52 ± 6	3.2 ± 0.3
22	Multiple sclerosis, age 22 to 59	53 ± 3	3.0 ± 0.2

TABLE 6

EFFECT OF INTRAVENOUS SODIUM SUCCINATE ON CEREBRAL METABOLIC RATES IN MULTIPLE SCLEROSIS

	Ml. or mg./100 gm. Brain/Min.		
	Control	*After Succinate*	*Number of Cases*
CBF	53 ± 3	57 ± 3	22
CMR O_2	3.0 ± 0.2	3.3 ± 0.2	22
CMR CO_2	−3.0 ± 0.2	−3.0 ± 0.4	22
CMR glucose	4.3 ± 0.5	4.9 ± 1.3	7
CMR pyruvate	0 ± 0.1	0 ± 0.1	7
CMR lactate	−0.2 ± 0.2	−0.1 ± 0.3	7

DISCUSSION

The data presented indicate that in normal human subjects there is an uptake of glutamic acid by the brain and a corresponding release of its amide glutamine. This process, which we may call amidation, appears to be lacking in patients with multiple sclerosis, particularly those who show signs of active progression of the disease. This defect in the process of amidation of glutamic acid to glutamine can be corrected in part by the intravenous administration of sodium succinate. The duration of this effect is not known, nor is any therapeutic implication to be assumed. Krebs[11] and Weil-Malherbe[12] have shown that amidation occurs in brain tissue in vitro. These workers have demonstrated that an external source of energy is needed for the reaction to proceed. It is likely that succinate may act as such a source of energy in patients with multiple sclerosis. However, we have found no change in the net uptake of glucose by the brain or in the release of lactic acid from the brain in multiple sclerosis before or after the administration of succinate. This suggests that succinate complements glucose as an energy source. A difference between the rates of utilization of glucose and of succinate cannot be excluded as an explanation for the effect of succinate, since the effect of increased concentrations of glucose has not been studied.

From the work of Krebs[11] and of Weil-Malherbe,[12] it appears that amidation is a method by which the brain rids itself of ammonia. Our data raise the possibility that the defect in cerebral amidation of glutamic acid to glutamine observed in multiple sclerosis may lead to accumulation of ammonia in the brain. The recent work of Bessman, Fazekas, and Bessman[13] and of McDermott and Adams[14] shows a relationship between high blood ammonia levels and impaired cerebral function in patients with Eck fistulas. These observations suggest the possibility, yet to be explored, that a defect in cerebral metabolism of ammonia may play a role in the pathogenesis of multiple sclerosis.

SUMMARY

1. The cerebral metabolism of 19 normal subjects and 32 patients with multiple sclerosis has been studied by the Kety-Schmidt technic, with special reference to the cerebral metabolism of glutamic acid and its amide glutamine. Measurements of cerebral metabolic rates for oxygen, carbon dioxide, glucose, pyruvic acid, and lactic acid have also been made.

2. Amidation of glutamic acid to its amide glutamine was found in 15 of 19 normal subjects.

3. Failure of amidation occurred in all but five of 32 patients with multiple sclerosis.

4. Intravenous administration of sodium succinate reversed the defect in the direction of amidation or utilization in half of the patients with multiple sclerosis.

5. It is suggested that the failure of glutamic amidation in patients with multiple sclerosis may reflect a failure of one mechanism for elimination of ammonia from the brain.

Grateful acknowledgment is made to Dr. Robert Aird for supplying many of the well documented cases of multiple sclerosis.

The heparin (Liquaemin-Organon) used in the cerebral blood flow studies was furnished by Dr. Kenneth Wade Thompson, Organon, Inc., Orange, N. J.

REFERENCES

1. KETY, S. S., and SCHMIDT, C. F.: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations, Am. J. Physiol. 143:53, 1945.
2. SCHEINBERG, P., and STEAD, E. A., JR.: The cerebral blood flow in male subjects as measured by the nitrous oxide technique. Normal values for blood flow, oxygen utilization, glucose utilization, and peripheral resistance, with observations on the effect of tilting and anxiety, J. Clin. Investigation 28:1163, 1949.
3. PETERS, J. P., and VAN SLYKE, D. D.: Quantitative Clinical Chemistry, ed. 2, Baltimore, Williams and Wilkins Co., 1946, vol. 1.
4. KETY, S. S., and SCHMIDT, C. F.: The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedures and normal values, J. Clin. Investigation 27:476, 1948.
5. NELSON, N.: A photometric adaptation of the Somogyi method for the determination of glucose, J. Biol. Chem. 153:375, 1944.
6. SOMOGYI, M.: A new reagent for the determination of sugars, J. Biol. Chem. 160:61, 1945.
7. HARPER, H. A.: The microbiological determination of glutamine in human plasma, Arch. Biochem. 15:433, 1947.
8. FRIEDEMANN, T. E., and HAUGEN, G. E.: Pyruvic acid. II. The determination of keto acids in blood and urine, J. Biol. Chem. 147:415, 1943.
9. MILLER, B. F., and MUNTZ, J. A.: A method for the estimation of ultramicro quantities of lactic acid, J. Biol. Chem. 126:413, 1938.
10. TUCKER, W. M., DONALD, D. C., JR., and FARMER, R. A.: Cerebral blood flow in multiple sclerosis, A. Res. Nerv. & Ment. Dis., Proc. 28:203, 1952.
11. KREBS, H. A.: Metabolism of amino-acids. IV. The synthesis of glutamine from glutamic acid and ammonia, and the enzymic hydrolysis of glutamine in animal tissues, Biochem. J. 29:1951, 1935.
12. WEIL-MALHERBE, H.: Significance of glutamic acid for the metabolism of nervous tissue, Physiol. Rev. 30:549, 1950.
13. BESSMAN, S. P., FAZEKAS, J. F., and BESSMAN, A. N.: Uptake of ammonia by the brain in hepatic coma, Proc. Soc. Exper. Biol. & Med. 85: 66, 1954.
14. MCDERMOTT, W. V., JR., and ADAMS, R. D.: Episodic stupor associated with an Eck fistula in the human with particular reference to the metabolism of ammonia, J. Clin. Investigation 33:1, 1954.

■ From the subsequent affection of the lower extremities, and from the failure of power in the muscles of the trunk, such a change in the substance of the medulla spinalis may be inferred, as shall have considerably interrupted, and interfered with, the extension of the nervous influence to those parts, whose nerves are derived from any portion of the medulla below the part which has undergone the diseased change.

The difficulty in supporting the trunk erect, as well as the propensity to the adopting of a hurried pace, is also referable to such a diminution of the nervous power in the extensor muscles of the head and trunk, as prevents them from performing the offices of maintaining the head and body in an erect position.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

Motor Epilepsy of Parietal Lobe Origin in the Monkey

Joseph G. Chusid, M.D., Lenore M. Kopeloff, Ph.D. and Nicholas Kopeloff, Ph.D.

THE APPLICATION of alumina cream to cerebral motor or sensorimotor cortex has proved highly effective in the production of chronic experimental epilepsy in the monkey.[1,2] A review of the effects of multiple intracerebral injections of alumina cream indicated that intracortical injections of alumina cream into a parietal lobe might also produce chronic epilepsy.[3] A study was therefore undertaken of the effects of intraparietal lobe injections of alumina cream in ten monkeys.

METHOD

Alumina cream was injected into the exposed parietal lobe cortex of a cerebral hemisphere in ten Macaca mulatta (figure 1). Five to eight injections were made slowly through a 26 gauge hypodermic needle to a depth of approximately 5 mm. and the amount of alumina cream retained was estimated at from 0.35 to 0.5 ml. In four monkeys ablation of adjacent precentral motor cortex was carried out six to ten weeks later (after the onset of seizures); in one monkey ablation of precentral motor cortex and intraparietal alumina injections were performed at the same time. Animals were observed following injections for periods up to 23 months, during which time clinical observations, serial electroencephalograms, and motion picture studies were made. Brains were studied post mortem, following which injected sites and ablated areas were mapped.

RESULTS

All ten monkeys in which alumina cream had been injected into a parietal lobe manifested clinical epilepsy after a seizure-free period of three to seven weeks. The initial detectable response in some consisted of contralateral, spontaneous tremulous motor activity and contralateral twitch-like movements of muscles with aggravation and accentuation to major convulsive seizures by jacksonian spread, particularly following excitement, agitation, or movement. Onset of seizures in others was heralded by focal contralateral clonic movements

From the department of bacteriology, New York State Psychiatric Institute, and the neurologic division, St. Vincent's Hospital, New York City.

Aided in part by a research grant from the National Institute of Mental Health, U.S.P.H.S., Bethesda, Maryland.

Presented before the American League Against Epilepsy, Washington, D.C., May 1, 1954.

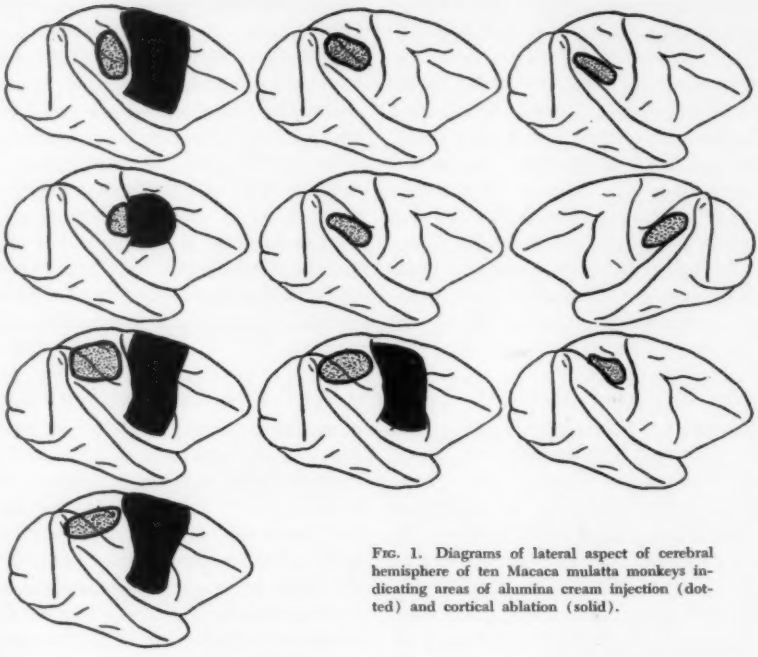


FIG. 1. Diagrams of lateral aspect of cerebral hemisphere of ten Macaca mulatta monkeys indicating areas of alumina cream injection (dotted) and cortical ablation (solid).

in limb or face, with frequent rapid jacksonian spread. In all animals focal motor seizures could be readily elicited or reproduced by intramuscular injections of pentamethylenetetrazole (Metrazol) in dosage up to 24 mg. per kg. Repeated seizures in any single treated animal were not always precisely the same, although contralateral focal onset was the rule. Qualitatively the seizures appeared to resemble those occurring in monkeys following alumina cream treatment of precentral motor cortex. The ablation of large portions of ipsilateral precentral motor cortex did not appear to alter significantly the convulsive response following intraparietal cortical injections of alumina cream. Seizures which could be regarded as purely, predominantly, or initially sensory in nature were not recognized as such.

Following intraparietal injection of alumina cream, little change in external appearance or behavior could be detected other than the occasional presence of a mild grade of hypotonia of contralateral limbs. After ablation of precentral motor cortex, there was contralateral moderate hemiparesis, hyperreflexia, spasticity with mild to moderate muscular atrophy, and contracture.

DISCUSSION

Contralateral focal motor seizures with jacksonian spread occurred in all animals treated by intraparietal cortical in-

jections of alumina cream. On occasion the initial epileptic manifestations resembled those usually seen following multiple intracerebral injections into relatively widespread areas of a principal sensorimotor cortex (epilepsia partialis continua).[3] In cases where the site of injection was into the parietal opercular area, an occasional seizure was observed to start with focal contralateral clonic or other movements of a lower extremity, suggesting the possibility of activation of efferent fibers from the second motor cortex situated in and near the infraparietal plane.

All of the treated monkeys were readily provoked into focal motor seizures by the intramuscular injection of pentamethylenetrazole. Whereas normal unoperated monkeys require 48 mg. per kg. or more,[4] all treated animals reacted to doses of 24 mg. per kg. or less. In four animals in which the minimal or threshold dose required to provoke convulsions was determined, the values obtained (8, 8, 12, 24 or less mg. per kg.) were in the same range as those found for monkeys made epileptic by application of a disk with alumina cream to a precentral motor cortex. Intramuscular injection of Metrazol was more effective in precipitating seizures than stress stimulation consisting of severe noisy prodding.

Despite the fact that the parietal lobe of the monkey is believed to contain the principal and much of the second sensory cortex, we were unable to detect or recognize the presence of purely or predominantly sensory seizures or auras in this group of treated animals. We believe, however, that macaque monkeys might well have sensory seizures or auras without their being apparent from external observation or examination, so that the possibility of such seizures or auras cannot be excluded. Since the inherent difficulties associated in dealing with subjective or sensory states in the monkey are enormous, the question arises as to how indeed the presence of changes could ever be reliably detected. The problem becomes even more difficult if it is accepted that motor responses may also occur following activation of the area in question. The observations of Clark and Ward[5] may be cited in this connection. They found that upon electrical stimulation of the cortex of unanesthetized monkeys by means of implanted electrodes, the usual response to parietal (as well as precentral) cortical stimulation was motion. Analysis of their illustrations and maps indicates that movements were elicited upon electrical stimulation from all their 107 implanted electrodes, 30 of which were in the parietal lobes; responses that could be interpreted as sensory in nature occurred from stimulation of only five of these electrodes, which were located in a small portion of the postcentral region.

Evidence for motor representation within the parietal lobe of the monkey may be cited from several sources. Ferrier[6] was the first to report that direct electrical stimulation of the exposed parietal cortex produced motor effects. Graham Brown[7] demonstrated that cortical stimulation of a parietal lobe could facilitate motor responses to subsequent stimulation of precentral motor cortex. Woolsey[8] and his collaborators reported for the postcentral gyrus of the monkey a detailed pattern of representation of contralateral skeletal musculature, paralleling the pattern for touch representation. Their studies, made on chronic monkeys after bilateral precentral motor and supplementary motor area ablations, suggest that a motor pathway from the

postcentral gyrus exists which is entirely independent of pathways originating precentrally. Sugar, Chusid, and French[9] described a second motor cortex in the monkey, lying on the lateral and medial wall of the frontoparietal operculum and the posterior portion of the insula, with arrangement of body parts essentially as in the second sensory area and which produced characteristic motor responses upon electrical stimulation. Woolsey and Chang[10] stimulated electrically the medullary pyramids and showed that antidromic pyramidal tract volleys could be recorded from large expanses of the postcentral as well as the precentral gyri. According to Lilly[11] analysis of the recordings of "electrical figures" in the pre- and postcentral gyri of unanesthetized monkeys obtained with 25 implanted electrodes indicates the presence of a postcentral motor representation, which is a mirror image of the precentral one.

It has been observed that ablation of portions of the parietal lobe cortex of the monkey may affect motor function significantly. Peele[12] characterized the effect of parietal lobe ablation in the macaque as a "loatheness for movement." Kennard and Kessler[13] reported motor disability characterized by relative disuse of the operated as compared with the normal extremity following parietal lobe ablation. Welch and Kennard[14] noted that the ablation of postcentral gyrus added to ablation of precentral motor areas producing spasticity, increased the monkey's paresis. Cole and Glees[15] stated that lesions in areas 3, 1, and 2 in monkeys trained for tests of discrimination by palpation, dexterity, and motor power caused some loss of motor power and dexterity.

Histologic studies also suggest a role for the parietal cortex in motor activity in the monkey since corticofugal connections via pyramidal and extrapyramidal pathways have been reported. Levin and Bradford[16] traced the origin of the corticospinal tract in the monkey by means of retrograde cell degeneration in the cerebral cortex after hemisection of the spinal cord and reported that an appreciable portion (almost 20 per cent) arose within areas 3, 1, 2, and 5 of the parietal lobe. Both Mettler[17] and Peele[18] reported that corticofugal fibers proceed from parietal cortex to subcortical areas including the substantia nigra, pontine nuclei, red nucleus, oculomotor complex, and superior colliculi. Uesugi's[19] Marchi studies indicated that the postcentral gyrus gives rise to corticospinal fibers and fibers to the substantia nigra, pontine nuclei, Forel's fields, and red nucleus. Sunderland[20] also described pontine fibers of postcentral origin, while Cole and Glees[15] noted descending fibers to the spinal cord originating in parietal lobe cortex.

SUMMARY

1. Chronic epilepsy occurred after a seizure-free interval of three to seven weeks in a group of ten Macaca mulatta treated by injection of alumina cream into a parietal lobe.

2. Focal contralateral motor convulsions with jacksonian spread occurred spontaneously, or could be induced by stress or intramuscular injections of Metrazol.

3. Ablation of ipsilateral precentral motor cortex in five of this group did not prevent motor seizures.

4. Evidence suggesting a role for the parietal lobe of the monkey in motor activity is cited.

REFERENCES

1. Kopeloff, L. M., Barrera, S. E., and Kopeloff, N.: Recurrent convulsive seizures in animals produced by immunologic and chemical means, Am. J. Psychiat. 98:881, 1942.
2. Kopeloff, L. M., Chusid, J. G., and Kopeloff, N.: Chronic experimental epilepsy in Macaca mulatta, Neurology 4:218, 1954.
3. Chusid, J. G., Kopeloff, N., and Kopeloff, L. M.: Experimental epilepsy in the monkey following multiple intracerebral injections of alumina cream, Bull. New York Acad. Med. 29:898, 1953.
4. Chusid, J. G., Kopeloff, L. M., and Kopeloff, N.: Convulsive threshold values to parenterally injected pentamethylenetetrazole in epileptic monkeys, J. Appl. Physiol. 6:139, 1953.
5. Clark, G., and Ward, J. W.: Responses elicited from the cortex of monkeys by electrical stimulation through fixed electrodes, Brain 71:332, 1948.
6. Ferrier, D.: The Functions of the Brain, London, Smith, Elder & Co., 1876. p. 323.
7. Brown, T. Graham: Studies in the physiology of the nervous system. XXVII. On the phenomenon of facilitation, Quart. J. Exper. Physiol. 10:103, 1916.
8. Woolsey, C. N., Travis, A. M., Barnard, J. W., and Ostenso, R. S.: Motor representation in the postcentral gyrus after chronic ablation of precentral and supplementary motor areas, Federation Proc. 12:160, 1953.
9. Sugar, O., Chusid, J. G., and French, J. D.: A second motor cortex in the monkey (Macaca mulatta), J. Neuropath. & Exper. Neurol. 7:182, 1948.
10. Woolsey, C. N., and Chang, H. T.: Activation of the cerebral cortex by antidromic volleys in the pyramidal tract, A. Res. Nerv. & Ment. Dis., Proc. 27:146, 1948.
11. Lilly, J. C.: Significance of motor maps of the sensorimotor cortex in the conscious monkey, Federation Proc. 12:87, 1953.
12. Peele, T. L.: Acute and chronic parietal lobe ablations in monkeys, J. Neurophysiol. 7:269, 1944.
13. Kennard, M. A., and Kessler, M. M.: Studies of motor performance after parietal ablations in monkeys, J. Neurophysiol. 3:250, 1940.
14. Welch, W. K., and Kennard, M. A.: Relation of cerebral cortex to spasticity and flaccidity, J. Neurophysiol. 7:255, 1944.
15. Cole, J., and Glees, P.: Effects of small lesions in sensory cortex in trained monkeys, J. Neurophysiol. 17:1, 1954.
16. Levin, P. M., and Bradford, F. K.: The exact origin of the cortico-spinal tract, J. Comp. Neurol. 68:411, 1938.
17. Mettler, F. A.: Corticofugal fibre connections of the cortex of Macaca mulatta. The parietal regions. J. Comp. Neurol. 62:263, 1935.
18. Peele, T. L.: Cytoarchitecture of individual parietal areas in the monkey (Macaca mulatta) and the distribution of the efferent fibres, J. Comp. Neurol. 17:693, 1942.
19. Uesugi, M.: Ueber die corticalen extrapyramidalen Fasern aus den sogenannten sensiblen Rindenfeldern (areae 1 und 2) beim Affen, Anat. Anz. 84: 179, 1937.
20. Sunderland, S.: The projection of the cerebral cortex on the pons and cerebellum in the macaque monkey, J. Anat. 74:201, 1940.

■ From the impediment to speech, the difficulty in mastication and swallowing, the inability to retain, or freely to eject, the saliva, may with propriety be inferred an extension of the morbid change upwards through the medulla spinalis to the medulla oblongata, necessarily impairing the powers of the several nerves derived from that portion into which the morbid change may have reached.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

Nature and Extent of the Biochemical Lesion in Human Epileptogenic Cerebral Cortex

An Approach to Its Control In Vitro and In Vivo

Donald B. Tower, M.D., Ph.D.

THIS paper summarizes present results of investigations into the biochemical bases for the spontaneous, paroxysmal neuronal discharge, which is the hallmark of seizures. In the first portion of the paper, studies of the metabolic activity of epileptogenic cerebral cortex in vitro are reviewed. Although some of these data have already been reported elsewhere, they are briefly restated to provide a background for the subsequent data which comprise preliminary results of the application of in vitro findings to clinical control of seizures.

Details of methods employed have been omitted since they have been, or will be, described elsewhere, but the general method of in vitro study deserves mention because of its particular application to the problem. Samples of tissue for study are obtained while patients are under local anesthesia during operation for excision of focal cortical epileptogenic lesions. These samples are rated by criteria previously adopted, based on electrocorticographic activity, response to direct electrical stimulation, and gross pathologic appearance.[1] After excision, the samples are sliced to an optimal thickness of 0.5 mm., using a Stadie-Riggs type fresh-tissue microtome, weighed on a torsion balance, and placed in Warburg flasks containing a nutrient saline medium with glucose and bicarbonate buffer which closely resembles natural brain fluid.[2] The vessels are then gassed with an optimal mixture of 95 per cent oxygen–5 per cent carbon dioxide and incubated at 38° C. for 60 minutes. One set of slices for each determination is removed at the start of incubation to serve as the initial or control level for the metabolic reaction under study. By treating all slices, epileptogenic and non-epileptogenic alike, in exactly the same manner, relative meas-

From the section of clinical neurochemistry, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

Read before the sixth annual meeting of the American Academy of Neurology, Washington, April 30, 1954.

These studies were begun at the Montreal Neurological Institute in association with Drs. Wilder Penfield, K.A.C. Elliott, Donald McEachern, and Guy Courtois, and are continuing at the National Institute of Neurological Diseases and Blindness in association with Drs. Maitland Baldwin, G. Milton Shy, Laurence Frost, and Leonard Berg.

TABLE 1
ACETYLCHOLINE METABOLISM IN HUMAN CEREBRAL CORTEX

Sample	Cholinesterase activity (μl. CO_2/g./hr.)	Incubated Slices—μg./g./hr. Free acetylcholine production 3 mM K+	Free acetylcholine production 27 mM K+	Change in bound acetylcholine 3 mM K+	Change in bound acetylcholine 27 mM K+
Non-epileptogenic (8)	0.95	0.25	1.9	+1.15	+0.55
Focal epileptogenic (17)	1.25	0.3	1.65	+0.3	0.0
+ Anesthesia in vivo (2)		–	1.85	–	+1.15
+ 10 mM L-glutamine or L-asparagine in vitro (8)*		0.2	1.85	+0.9	+0.85
+ 3 mM ATP in vitro (1)*		–	1.8	–	+0.6

Numbers in parentheses indicate number of samples.
*No effect on metabolism of non-epileptogenic samples.

ures of the capacity of respective slices to carry out metabolic reactions can be directly compared.

The use of fresh tisue slices, in which the integrity of the cell bodies is maintained, provides a close analogy in vitro to the in vivo situation. Only the elements of capillary circulation (which is compensated for) and neuronal activity (which can be artificially reproduced to some extent[3]) are lacking. This technic has proven invaluable for study of unstable or rapidly metabolized compounds and complex reactions, which may be lost or modified by methods involving fragmentation or disintegration of tissue elements. The data summarized below have all been obtained from tissue samples treated in this fashion and then preserved and analyzed by appropriate technics which are detailed elsewhere.[2,4–6]

THE BIOCHEMICAL LESION IN VITRO

The components of the biochemical lesion in human epileptogenic cerebral cortex include at least three of the important metabolic systems of cerebral tissue. The evidence for and the nature of these defects in metabolism can be briefly summarized in the following manner.

Acetylcholine Metabolism

In the acetylcholine system two abnormalities are present[1] as reviewed in table 1. Of the two, the more significant seems to be the failure of epileptogenic slices to show the increase in levels of bound acetylcholine found in non-epileptogenic slices.* It has been previously suggested[1] that this impairment in acetylcholine-binding capacity may result in a tendency in vivo for acetylcholine to be liberated unusually readily. There is some indirect support for this view.[7–9] Increased cholinesterase activity might be regarded as an attempted compensation for this abnormality.[1,10] Whatever the ultimate interpretation, these defects in acetylcholine metabolism represented the first chronic lesion to be demonstrated in human epileptogenic cortex, providing many of the clues to subsequent studies.

Means for control or reversal of these abnormalities of acetylcholine metabo-

*Bound acetylcholine has been previously defined as "the amount of acetylcholine which is held in the slice, presumably in an insoluble, inactive form, but which is liberated in active form on homogenization and treatment with dilute acid."[2]

TABLE 2
GLUTAMIC ACID AND GLUTAMINE METABOLISM IN HUMAN CEREBRAL CORTEX

Sample	*Incubated Slices—μM./g.*									*Incubation Medium*		
	Glutamic acid			*Glutamine*			*Total*					
	Initial	*60 min.*	*Change*	*Initial*	*60 min.*	*Change*	*Initial*	*60 min.*	*Change*	*Initial*	*60 min.*	*Change*
Non-epileptogenic (3)	8.45	9.9	+1.45	2.95	4.8	+1.95	11.4	14.7	+3.3	4.65	2.15	−2.5
Focal epileptogenic (7)	7.0	4.75	−2.25	3.05	5.25	+2.2	10.05	10.0	−0.05	4.4	2.6	−1.8
+10 m*M* L-asparagine in vitro*	–	7.25	(+1.0)	–	6.1	(+2.4)	–	13.35	(+3.4)	–	3.8	(−1.0)
+3 m*M* ATP in vitro*	–	9.6	(+1.75)	–	4.45	(+1.65)	–	14.05	(+3.4)	–	1.2	(−3.0)
+10 m*M* αketoglutarate in vitro*	–	8.9	(+2.65)	–	5.2	(+1.5)	–	14.1	(+4.15)	–	2.35	(−2.45)

All samples run with 27 m*M* K+ in medium.
Values in parentheses represent changes from control slices, where no initial slice was used for in vitro addition studies.
*No effect on metabolism of non-epileptogenic samples.

lism have been reported[4] and are also summarized in table 1. Anesthesia in vivo, which normally enhances the capacity of slices to bind acetylcholine, results in some rise in bound acetylcholine levels but not to the degree normally encountered. In contrast L-glutamine or L-asparagine, which have no effect when added in vitro to non-epileptogenic slices, reverse the failure of epileptogenic slices to bind acetylcholine. This is also true for in vitro addition of adenosine triphosphate (ATP). Glutamic acid proved ineffective under these conditions.

Glutamic Acid and Glutamine Metabolism

As a result of the above findings with glutamine and because of the prominent position of glutamic acid in nervous tissue metabolism,[11] the metabolism of these two compounds in human epileptogenic cortex was studied under conditions identical to those used for acetylcholine. The findings summarized in table 2 indicate that in this metabolic system is situated the second component of the biochemical lesion.[5,12]

In non-epileptogenic slices, there is an initial loss of glutamine* into the incubation medium before optimal conditions are established, and the glutamic acid and glutamine levels in the slices are low. By the end of incubation the slices have taken up glutamine from the medium, and both glutamic acid and glutamine levels in the slices have risen to expected levels of 10 μM./g. and 5 μM./g. respectively, or a total of 15 μM./g.[13]

For the epileptogenic slices, the situation initially is essentially similar with a tendency for the glutamic acid level to be somewhat lower. At the end of incubation these slices have also taken up glutamine from the medium with a rise in the slice level, but the level of glutamic acid has fallen to approximately one-half the expected level of 10 μM./g. Since this reduction in glutamic acid during incubation cannot be accounted for by a loss externally to the incubation medium (either as glutamic

*Analytical evidence indicates that most of the activity in the incubation medium is glutamine, although paper chromatograms suggest some of the total may be glutamic acid.

TABLE 3
ELECTROLYTE METABOLISM IN HUMAN CEREBRAL CORTEX

Sample	Incubated Slices – μEq./g.* Potassium Initial	Potassium 60 min.	Potassium Change	Sodium Initial	Sodium 60 min.	Sodium Change	Total Initial	Total 60 min.	Total Change
Non-epileptogenic (2)	71.5	95.5	+24.0	90.0	65.5	–24.5	161.5	161.0	–0.5
Focal epileptogenic (2)	63.5	69.5	+6.0	92.0	83.0	–9.0	155.5	152.5	–3.0
+10 mM L-asparagine in vitro**	–	105.5	(+37.0)	–	46.0	(–48.5)	–	151.5	(–11.5)

*Incubation medium contained: K+ 27 μEq./ml.; Na+ 123 μEq./ml.
All samples corrected for adherent medium (see text).
Corresponding changes observed in incubation media for both K+ and Na+.
**No effect on metabolism of non-epileptogenic samples.

acid or its two principal metabolic products, γ-aminobutyrate or α-ketoglutarate), this represents an internal loss within the tissue or what Krebs[14] has termed a "metabolic" loss.

As for acetylcholine metabolism, the addition in vitro of L-asparagine, ATP, and also α-ketoglutarate all promote an increase in glutamic acid levels of epileptogenic slices while none affect metabolism of non-epileptogenic slices. These studies, still in progress, will be reported more completely in a subsequent paper.[5]

Potassium and Sodium Metabolism

An association between levels of electrolytes and of glutamic acid in cerebral cortex has been recently proposed.[15] Because of the implications of the findings in table 2 in this regard together with the established importance of potassium in neuronal activity, the metabolism of potassium and sodium in epileptogenic cortex is now under study by methods identical to those used in the two foregoing studies. Present results are given in table 3. Because of the analytical difficulties involved, these results are subject to some reservation.* However, there appears to be a striking difference between the two types of slices. In both cases, potassium is lost initially to the incubation medium with a corresponding replacement by sodium in the tissue prior to establishment of optimal conditions. During incubation, non-epileptogenic slices take up the lost potassium and expel the excess sodium into the medium to achieve the expected concentrations of these two cations within the tissue of approximately 100 μEq./g. K+ and 60 μEq./g. Na+.[15,16] In contrast epileptogenic slices are apparently unable to accomplish this exchange, retaining abnormally low potassium and high sodium levels throughout. Addition of L-asparagine in vitro does not affect non-epileptogenic slices but permits epileptogenic slices to reconcentrate potassium with corresponding extrusion of sodium. Investigation of these findings is continuing and will be reported in detail subsequently.[6]

*In the analysis it is necessary to correct for the cation concentration contributed by incubation medium adherent to tissue slices. Classically, this correction is made by determining the weight increase of the slice during incubation, assuming all the increase to represent adherent medium.[15] The validity of this method of correction has never been established. Until results of studies now in progress to test this validity are obtained, the findings in table 3 remain subject to certain reservations. It should be noted that these considerations do not apply to other studies presented here.

TABLE 4
CAT CEREBRAL CORTEX
Slices – Incubated 60 minutes

Determinations	Experimental Conditions: Normal	Methionine sulfoximine (in vivo)	Partial anoxia (in vitro)
1. Change in Bound Acetylcholine:			
Control	+2.55	+0.05	+0.05
+ Anesthetics or anticovulsants in vivo	+3.9	+1.75	+2.2
+ 10 m*M* L-glutamine or L-asparagine in vitro	+2.55	+2.2	+2.65
+ 3 m*M* ATP in vitro	+2.2	–	+2.2
2. (a) Level of Glutamic Acid:			
Control	8.95	4.95	5.25
+ Anesthetics in vivo	9.5	–	–
+ 10 m*M* L-asparagine in vitro	9.2	8.5	8.6
+ 3 m*M* ATP in vitro	8.45	7.75	8.85
(b) Level of Glutamine:			
Control	5.7	0.85	2.75
+ Anesthetics in vivo	6.15	–	–
+ 10 m*M* L-asparagine in vitro	4.6	0.0	2.85
+ 3 m*M* ATP in vitro	5.5	1.15	1.45
3. (a) Level of Potassium:	89.9	–	41.9
(b) Level of Sodium:	66.9	–	124.8

Units: Acetylcholine–μg./g./hr.; glutamic acid and glutamine–μ*M*./g.; sodium and potassium–μEq./g. All values are level or change at 60 min. incubation time.

Experimental Reproduction of Metabolic Abnormalities

Reproduction of the metabolic abnormalities discussed above has been accomplished experimentally in the cat, using two methods previously described.[4] The first of these employs the convulsant agent, methionine sulfoximine, inducing seizures in cats prior to sacrifice for cortical study. The other depends upon the incubation of slices of normal cat cortex under conditions of partial anoxia. Results of studies by these methods are summarized in table 4.

Both methods produce defects in metabolism of the slices which resemble those found in human epileptogenic cortical slices. In both cases there is failure of the acetylcholine-binding mechanism* and reduction in the glutamic acid levels in the slices and, under partial anoxia in vitro, inability of slices to regain potassium and expel sodium. Glutamine levels in these slices, however, are low compared to controls and to human cortical slices. In the case of methionine sulfoximine administration this is consistent with reports that the toxic agents or its derivatives inhibit glutamine synthesis.[18–20] With partial anoxia in vitro there is continued loss of glutamine to the incubation medium during incubation, suggesting interference with mechanisms concerned with maintenance of cell membrane integrity. Despite the three different mechanisms involved, low levels of glutamic acid are common to human epileptogenic coritcal slices and to slices of cat cerebral cortex either intoxicated by methionine sulfoximine or incubated under partial anoxia.

*Differences in acetylcholine values for human and cat cerebral cortex relate to dependence of acetylcholine activity upon brain size of respective species.[2,17] This is not a factor for either glutamic acid or electrolyte metabolism.

TABLE 5

COMPONENTS OF THE BIOCHEMICAL LESION IN HUMAN EPILEPTOGENIC CEREBRAL CORTEX

	Cortical Slices—incubated 60 min. (at 27 mM K+)				
Sample	Cholinesterase activity (μl. CO_2/g./hr.)	Change in bound acetylcholine* (μg./g./hr.)	Level of glutamic acid** (μM./g.)	Level of potassium (μEq./g.)	Level of sodium (μEq./g.)
Non-epileptogenic	0.93	+0.55	9.9	93.5	65.5
Focal epileptogenic	1.25	0.0	4.75	69.5	83.0

*Free acetylcholine production—no significant differences (1.9; 1.65).
**Glutamine levels—no significant differences (4.8; 5.25).

Anesthetics and also anticonvulsants (with the exception of the Tridione group) in vivo normally enhance the capacity of cortical slices to bind acetylcholine during incubation. By virtue of this characteristic, some correction of the defect in acetylcholine-binding produced both by methionine sulfoximine and by partial anoxia occurs after in vivo administration of an anesthetic or anticonvulsant. This increase in acetylcholine-binding does not equal control values so that this is only a partial correction. No significant effect of anesthesia on glutamic acid or glutamine metabolism of normal cortex is apparent. The in vitro addition of L-asparagine or of ATP to defective slices of cat cortex reverses the impairments of acetylcholine and of glutamic acid metabolism, but not of glutamine metabolism. These results are similar to those obtained with human epileptogenic cortex. Fuller consideration of these studies will be presented in later papers.[5,6]

The data summarized in table 4 exemplify the type of information which can be obtained by these approaches. Considerable insight into mechanisms by which abnormalities are produced and by which corrective effects are obtained can be gained by these experimental studies. The lack of truly normal human material and limitations in size of samples available limit such studies on human samples to final assessments of appropriate findings developed experimentally with cat cortex.

Summary of Studies on Human Cerebral Cortex

In table 5 the essential findings in regard to metabolic activity of slices of epileptogenic and non-epileptogenic cerebral cortex are summarized. The components of the biochemical lesion demonstrated so far include: 1) the acetylcholine system, with a slight, questionably significant increase in cholinesterase activity and a significant failure of the tissue to build up its level of bound acetylcholine; 2) the glutamic acid system, with a significant "metabolic" loss of glutamic acid during incubation; and 3) electrolyte metabolism, with an apparently significant reversal of normal potassium-sodium levels. These abnormalities are chronic in nature, persisting after excision of the tissue samples, in contrast to the many pathophysiologic changes present only during a seizure. These metabolic defects are reversible in vitro, indicating that they do not result from permanent structural changes but represent some type of functional interference with these metabolic systems. Specific studies show that these findings are not attributable to factors such as differences in cell density or cortical stimulation.[1,5]

The three metabolic systems significantly involved implicate indirectly a fourth system-complex concerned with energy metabolism. This conclusion is based upon the present concepts that the binding of acetylcholine, the maintenance and transport of glutamic acid and potassium in the cell, and the synthesis of glutamine all require energy in the form of high-energy phosphate from adenosine triphosphate (ATP) or creatine phosphate. The in vitro corrective effects of ATP and of α-ketoglutarate are consistent with this view. These metabolic abnormalities are consistent with instability of neurons, which is characteristic of epileptogenic brain areas, and they are apparently due primarily to a relative deficit in available energy, the nature and cause of which is not known.

What are the implications of these observations? In figure 1 a simplified diagram of many of the important metabolic interrelationships which occur in central nervous tissue is depicted. Centrally in this scheme is the Krebs tricarboxylic acid cycle of intermediary carbohydrate metabolism. It accepts pyruvate from glucose breakdown to effect the final breakdown of carbohydrate to carbon dioxide and water. In doing so it provides CO_2, important in regulation of tissue pH, and it augments the supplies of high-energy phosphate as ATP and creatine phosphate, the cells' immediate sources of energy for metabolic work. Intimately associated with this cycle are three carbohydrate-amino acid interchanges, pyruvate with α-alanine, oxaloacetate with aspartic acid, and α-ketoglutarate with glutamic acid. These involve relationships to protein metabolism via transamination, to ammonia metabolism, and possibly to potassium metabolism. A relationship to acetylcholine metabolism can be made only by inference at present.

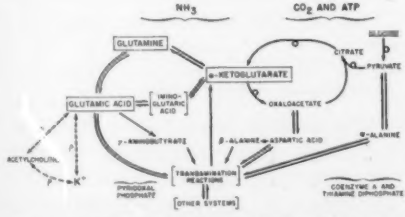


FIG. 1. Some important metabolic interrelationships in brain tissue, illustrating carbohydrate-amino acid interchanges. The convention ⟶ indicates intervening metabolic steps. Relationships between glutamic acid and K+ or acetylcholine are not yet established, as indicated by ⟵ ? ⟶. The coenzymes (below) and principal metabolites (above) concerned in these reactions are enclosed in horizontal braces.

Glutamic acid is situated at the metabolic crossroads in this scheme. Together with glutamine, it constitutes the majority of the intracellular nonprotein nitrogen of nervous tissue.[13] It is one of the major intracellular anions, apparently closely associated with the principal cation, potassium.[15] It is important as a protein building block. It has ready access to the Krebs cycle via α-ketoglutarate or via γ-aminobutyrate[21,22] and will, in fact, support nervous tissue metabolism for a brief time in the absence of carbohydrate energy sources.

Evidence is now appearing suggesting an importance for glutamic acid in seizures. One facet is the in vitro studies on human epileptogenic cerebral cortex reviewed above. The rather unique convulsant agent, methionine sulfoximine, has been shown by others and the present study to inhibit glutamine synthesis and to be associated with low levels of glutamic acid. Reduced levels of glutamic acid in rat brain have been reported to be associated with strychnine convulsions.[23] Fluoroacetate poisoning, which has been shown to block the Krebs cycle at the citrate stage[24] and

which produces convulsions in many species, has been shown to be associated with lowered levels of glutamic acid in various organs,[25] including cerebral tissue from the adult rat.[30] Pyridoxal phosphate, the coenzyme derived from pyridoxine (vitamin B_6) which catalyzes a number of reactions involving glutamic acid, has recently been implicated directly or indirectly in several seizure situations. Infants fed exclusively on SMA liquid formula have been reported to develop convulsions, now known to be due to deficiency of pyridoxine in the formula.[26] The hydrazides, including the antitubercular isonicotinic acid hydrazide (Isoniazide), which possess convulsant properties at toxic levels,[27] exhibit a competitive inhibition with pyridoxine for enzyme systems in which the latter is an essential component.[28] Desoxypyridoxine, the antimetabolite of pyridoxine, is reported to be a potent convulsant agent in experimental animals.[29] And a case of seizures is on record which is controllable only by regular administration of pyridoxine.[30]

All these observations focus on the general area of glutamic acid metabolism. It seemed worthwhile to try to increase the level of glutamic acid in affected neurons with the idea that this might compensate for or overcome defective metabolism and thus contribute to a more stable intracellular environment. The administration of glutamic acid itself to seizure patients will not accomplish this. Price, Waelsch, and Putnam[31] tried and many others followed with generally disappointing results. In the present investigation it was found to be ineffective in vitro.[4] It is clear that these failures have an explanation in findings that glutamic acid fails to penetrate the blood-brain barrier to any appreciable degree,[32–34] and that it may be slow to penetrate the cell membrane unless converted to a diffusible form.[35] Both glutamine and its next lower homologue, asparagine, have proven effective in vitro, as indicated earlier in this paper. Glutamine has been shown to penetrate the blood-brain barrier and cell membrane readily.[32–34] Therefore, it seemed worthwhile to assess the effectiveness of these two amino acid amides clinically on seizure patients.

PRELIMINARY OBSERVATIONS ON THE EFFECTS OF L-GLUTAMINE AND L-ASPARAGINE IN SEIZURE PATIENTS

Several studies on parenteral or oral administration of glutamine to various experimental animals have been published,[32–34] but no reports of its administration to man have been found. Data for asparagine, even in animal studies, are lacking. Experimentally it has been shown that glutamine is readily absorbed from the intestinal tract without hydrolysis,[34] so that it might be expected that asparagine, which is relatively more stable, would be similarly absorbed unchanged. Before undertaking clinical studies employing relatively large quantities of these two amides, further control studies in animals seemed desirable. These will be reported in detail elsewhere.[36]

Dosage and Preparations

The range of dosage has been derived empirically from observations of effect of amide concentration on reversal of the defect in acetylcholine-binding of cat cortex in vitro,[4] as reproduced in figure 2. In this series of experiments a concentration of 10 mM/kg. for either amide resulted in 100 per cent reversal,

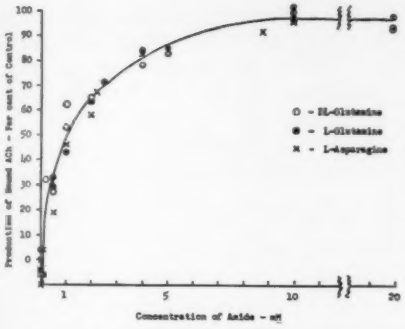


FIG. 2. The effects of varying amide concentrations, added to the incubation medium, on the increase in bound acetylcholine in slices of cat cerebral cortex incubated under conditions of partial anoxia. The control value is the increase obtained in slices incubated under optimal oxygenation. (Reproduced by permission of the *Journal of Applied Physiology*, 5:387, 1953.)

and a concentration of 2 mM/kg. produced a 50 to 60 per cent reversal. (1 mM of glutamine = 146 mg.; 1 mM of asparagine (anhydrous) = 132 mg.). The maximum solubility of either in aqueous solutions is barely 5 gm. per 100 ml. On the basis of these findings a dose of 2 mM/kg. of body weight (approximately 300 mg./kg.) was chosen for clinical trials. Control studies were accordingly related to this figure. More satisfactory methods for determination of dosage are now under study.*

In all cases the natural or L-forms of glutamine or asparagine have been used.† Anhydrous L-asparagine was always used because of its superior solubility to the less expensive monohydrate. Both amides, at present derived by isolation from natural sources, were purchased from chemical manufacturers. Purity of the preparations on analysis has always been at least 90 per cent, the residue being mostly if not all due to the parent acid. For *intravenous administration* asparagine can be made up to the desired concentration and autoclaved in standard fashion. Glutamine, because of the lability of its amide group, cannot be so prepared but must either be Seitz-filtered or treated in some analogous manner. In every case standard tests for sterility and freedom from pyrogens have been carried out. Our first glutamine solutions were prepared by Seitz filtration, but subsequently sterile ampules of glutamine powdered by a lyophylization procedure have been used. For *oral administration* the crystals have been used directly, as purchased, in both cases dissolved in a glassful of any appropriate liquid vehicle. Tomato juice is most satisfactory because of the greater solubility of the amides in it. Most patients have preferred solution in chocolate milk, satisfactorily accomplished by using a Waring-type blendor. Some care is necessary to avoid poor solution with loss of much of the dose as sediment in the glass. A flavored liquid suspension has now been developed which should prove more satisfactory to dispense.

Control Studies

Several types of observations in experimental animals have been carried out. Large series of mice were given methionine sulfoximine (150 mg./kg. body weight intraperitoneally) to induce seizures. After development of

*Despite the empirical nature of dosage, some observations during intravenous administration suggest that doses below 1.5 mM/kg. body weight fail to give expected changes and that doses in excess of 3 mM/kg. body weight fail to increase the degree of improvement attained. Preliminary studies, based on nonprotein nitrogen rise in serum after oral doses of asparagine, indicate that the maximum rise occurs between 60 and 120 minutes after ingestion and fasting levels appear to be reached after about four hours.

†DL-asparagine, which can be easily and cheaply synthesized, is under preliminary trial.

seizures the mice were randomly sampled into groups of controls injected with physiological saline, and groups injected with saline solutions of glutamine, asparagine, or glutamic acid (in concentration of 10 mM/kg. body weight). In contrast to the control mice and those receiving glutamic acid, which all died in status epilepticus, those receiving glutamine or asparagine survived seizure-free, provided they weathered the period immediately following injection before the amides could be absorbed and act.[36] Independent tests indicate that the LD_0 dose in mice for these amides exceeds 17 mM/kg. body weight.[37] Doses up to 10 mM/kg. injected intraperitoneally into unanesthetized *Macaca mulatta* monkeys were tolerated without visible reaction.

Systematic studies on dogs were then carried out. The dogs were anesthetized with Nembutal and recordings of carotid blood pressure, respiration, electrocardiogram, and electroencephalogram were made by standard technics.[36] Blood samples for appropriate chemical studies were drawn. After a period of control observation, large doses (6 to 8 mM/kg.) of either glutamine or asparagine in sterile solution were administered intravenously at a rapid rate. Recordings were continued during administration and up to three hours after completion, with blood samples for analysis drawn at intervals during this time. An example of the results obtained in these studies is shown in figure 3, in this case for glutamine. No significant changes in any recordings, with the exception of an expected rise in pulse pressure due to rapid infusion, were noted in repeated studies. The expected rise in blood nonprotein nitrogen occurred as a result of infusion but returned to control levels by 60 to 90 minutes after termination of the infusion. No significant changes in other blood constituents such as CO_2, electrolytes, glucose, or cell counts occurred. Entirely similar results were obtained repeatedly with asparagine.[36] Limited observations in human volunteers, using rapid infusion of doses approximating 2 mM/kg. during recording of electroencephalogram and electrocardiogram, with observations of blood pressure and respiration and studies of blood and urine constituents, also failed to reveal any significant deviations from control observations, except as anticipated by the nature of the infusion.[36] In no case were any side effects noted. On the basis of these studies it was deemed safe to undertake clinical trials.

Patient Selection and Methods of Study

The criteria for patient selection were three: 1) an established history of seizures, 2) prolonged trials on adequate anticonvulsant medication without satisfactory control, and 3) either frequent clinical seizures documented by history and by three or more weeks of ward observation, or relatively constant electroencephalographic abnormality on repeated recordings over a three week period or both. No attempt so far has been made to select particular types of seizures, although access to cases of focal cortical seizures has been necessarily limited by a surgical program for these patients also in progress.[38]

All patients have been admitted for ward observation, during which neurologic, radiologic, and electroencephalographic examinations are carried out. Complete studies of hematologic, renal, and hepatic function as well as of various blood chemistries are also conduct-

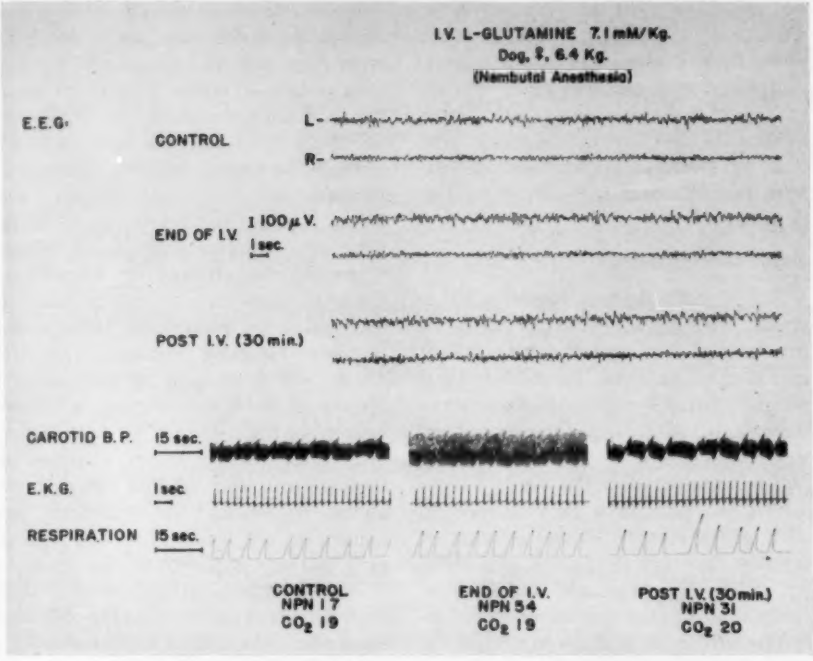


FIG. 3. The effect of intravenous administration of a solution of L-glutamine on electroencephalographic activity, electrocardiogram, blood pressure, and respiration of the anesthetized dog. Anesthesia was Nembutal (30 mg./kg.) intravenously, repeated as required. Dose of L-glutamine 7.1 mM/kg. (6.6 gm.) administered in a total volume of 125 ml. over a period of 20 minutes. Electroencephalogram recorded from needle electrodes placed symmetrically over both hemispheres. Electrocardiogram recorded from forearm leads. Blood pressure recorded from cannulated carotid artery by a metallic bellows manometer with ink-writer in parallel with a mercury manometer. Respiration recorded by an air tambour with ink-writer actuated by a Manning-type pneumograph. Units for blood chemistry levels are: Nonprotein nitrogen in mg./100 ml. and CO_2-combining power in mEq./liter.

ed. Two types of study have been carried out on patients selected. In appropriate patients the effects of intravenous administration of glutamine or asparagine during electroencephalographic recording have been investigated. In other patients, or in the same ones, the effects of oral asparagine on clinical course and on electroencephalographic abnormalities over a prolonged period of regular administration have been assessed. (Glutamine was not used in these latter series because of the high cost of the naturally isolated form. Synthetic glutamine at substantially less cost will shortly be in quantity production to permit use in such studies.)

Nine patients comprise the group used in this preliminary assessment. Their ages varied from nine to 39 years, with a sex distribution of six male and three female patients. With the exception of three patients with focal or suspected focal cortical seizures, all can be classified in the group of subcortical or centrencephalic seizures but only one could

be termed typical of classical 3/sec. spike and wave petit mal. Thus, the majority had a mixture of minor seizures (absences and akinetic in type) and major generalized seizures with grossly abnormal electroencephalograms typified by bilateral epileptiform activity with mixed cortical and subcortical components.

Intravenous Studies

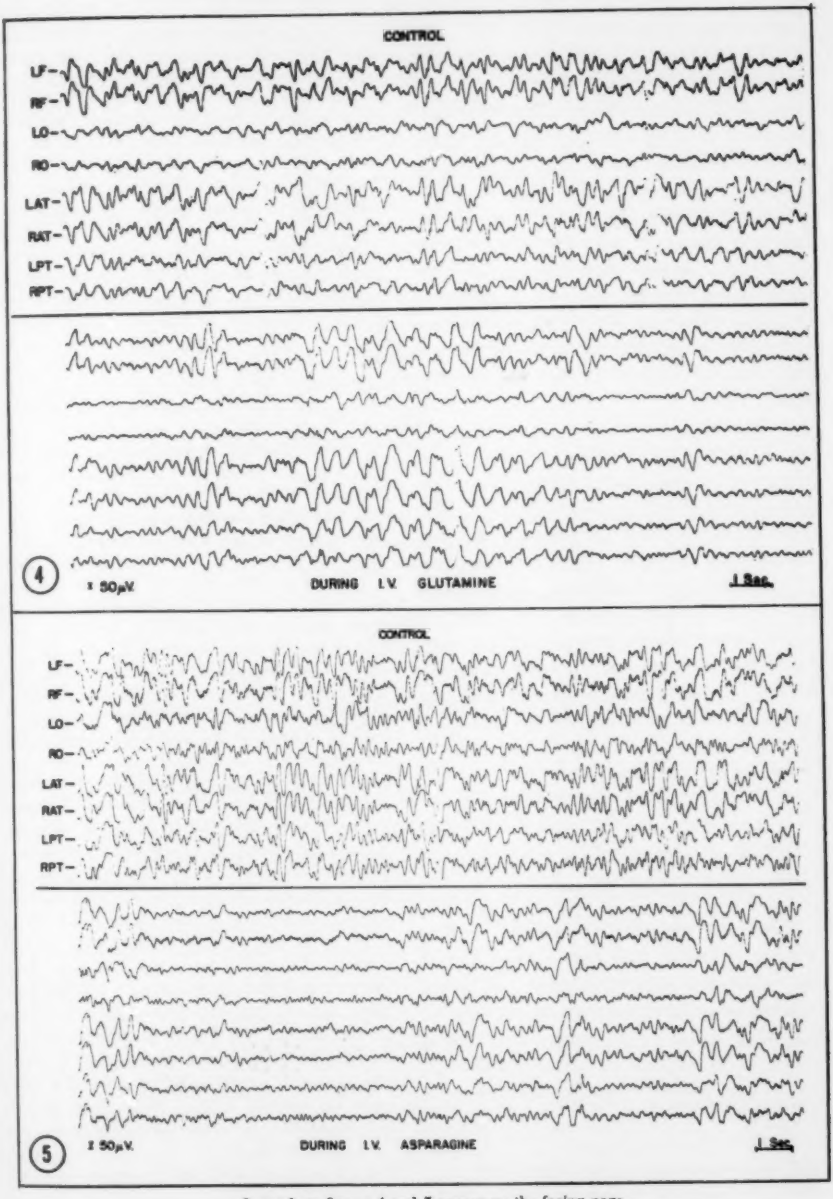
Six of the patients participated in studies with glutamine or asparagine intravenously. All received a dose on each occasion of at least 1 mM/kg. body weight. In four repeated observations were made. All tolerated the procedures well. Only those of particular interest will be considered at this time

The first patient, a 19 year old girl with mental retardation and generalized seizures since age five, developed status epilepticus spontaneously under observation. Asparagine was administered intravenously in an attempt to control the status twice in a period of 24 hours. The results were equivocal, probably for reasons which will be developed below. But it is of interest that this patient received a total of 42.5 gm. of asparagine (5.2 mM/kg. body weight) intravenously in a two hour period without incident.

Two patients, a nine year old boy and a nine year old girl respectively, received multiple infusions of both glutamine and asparagine. The boy had developed seizures at the age of four and electroencephalograms were available from that time on. Those and the records obtained under present observations all showed consistently highly abnormal activity from all leads with essentially no normal activity discernible. Examples are illustrated in figures 4 and 5 (top lines). During intravenous glutamine or asparagine a significant change occurred, characterized by intermittent shifts to more normal higher frequencies and lower amplitudes interspersed between typically abnormal activity. These periods of more normal activity, illustrated in figures 4 and 5 (lower lines), were never seen in control records. Detailed frequency analyses of these records showed that the shifts to higher frequencies were statistically significant in all leads ($P < 0.01$). One such analysis is illustrated in figure 6. The intermittent nature of the shift toward normal may explain the difficulty encountered in control of status epilepticus discussed above.

Similar findings were obtained for the nine year old girl. Analysis of her records could simply be made by plotting percentages of each minute of record occupied by abnormal activity. Such a plot for one lead is illustrated in figure 7. The recurring peaks of abnormality in the plot appear to be aborted and suppressed during and immediately after the amide infusion. This reduction in percentage of abnormal activity was

FIG. 4. The effect of intravenously administered L-glutamine on electroencephalographic activity of a seizure patient, J. W., male, age 9, weight 25 kg. Control record (top) obtained immediately prior to infusion. Record during infusion at bottom. All recordings made with scalp electrodes, referred to a common vertex lead, from left and right hemispheres (F—frontal; O—occipital; AT—anterior temporal; PT—posterior temporal). Dose of L-glutamine 1.5 mM/kg. (5 gm.) administered in a total volume of 150 ml. over a period of 15 minutes. The intervals of more normal activity appearing during intravenous glutamine are shown in the right half of the lower record.
FIG. 5. The effect of intravenously administered L-asparagine on electroencephalographic activity of a seizure patient. Same patient and recording conditions as in figure 4. Dose of L-asparagine 2.7 mM/kg. (10 gm.) administered in a total volume of 200 ml. over a period of 20 minutes. The intervals of more normal activity appearing during intravenous asparagine are shown in the left half of the lower record.



Legends to figures 4 and 5 appear on the facing page.

statistically significant ($P < 0.01$).

One other patient, a 39 year old man with focal seizures arising in the left temporal lobe, received 25 gm. of glutamine intravenously during electroencephalographic recording. This probably represents the largest amount of glutamine administerad to man up to the present time. It was entirely without incident. In this case during the infusion there was no discernible effect on spike activity but again a significant suppression of or shift from the very slow frequencies present in the control record.

A tentative conclusion which may be drawn from these studies is that intravenously administered glutamine or asparagine affects abnormally slow frequencies either by suppression or promotion of shift to higher frequencies. The possibility of an effect attributable to the solvent employed was ruled out by repeat trials in several patients with different solvents but similar results. No evidence has been found to indicate that infusion of volumes of fluid not exceeding 10 per cent of blood volume affect electroencephalographic activity per se. In no case was there a discernible reduction in the extent of spike activity.

Oral Asparagine Studies

Five patients are participating in this study, including two who also took part in intravenous observations. All were started on a dosage schedule of 2 mM/kg. body weight four times daily (taken with meals and at bed time), although some adjustments were found desirable subsequently.

Case 1.—The first patient is the nine year old boy whose intravenous studies are illustrated in figures 4, 5, and 6. Since onset of seizures at age four, his history has been exceptionally well-documented clinically and electroencephalographically. Despite adequate trials on anticonvulsant medication of various types, he continued to have several major generalized seizures and numerous minor akinetic seizures daily. Coincidentally he had a slow, slurred speech and certain awkwardness of fine movements, and, despite good intelligence, had never been able to attend school regularly or participate in usual boyhood activities because of seizure frequency. In 53 days of close observation while on his usual medication (Hibicon and Mebaral) he had at least 113 major seizures. Minor seizures could not be recorded accurately but were very frequent daily, often complicated by physical injury from the falls.

He was placed on asparagine 2 mM/kg. body weight (7 gm.) four times daily by mouth in addition to his regular medication and has now been on this regime for more than six months. In the first 120 days he had only 114 major seizures, representing a reduction of over 50 per cent in number. In addition it was clear that the severity of these seizures was much less than those in the control period. During the next month only 16 major seizures were recorded. From an average of two or three seizures per day, the frequency has dropped to less than one per day. The minor akinetic seizures virtually ceased. That this change can be attributed to asparagine is attested to by two facts. No previous combinations of medication had achieved this degree of improvement. During a three week period when the patient inadvertently received the relatively insoluble asparagine monohydrate, which was only poorly taken, his seizure frequency reverted to its previous level and then promptly improved when more soluble anhydrous asparagine was substituted. Less tangible is the general improvement in this patient. His speech has quickened and much awkwardness has disappeared. He is more alert. His appetite has improved and he has gained weight. He has been able to resume schooling regularly and participate in social activities such as cub scouts for the first time since his seizures began. How much of this is attributable to reduction in seizures and how much to asparagine per se is conjectural. The patient has continued to improve to a degree which permitted omission of Hibicon

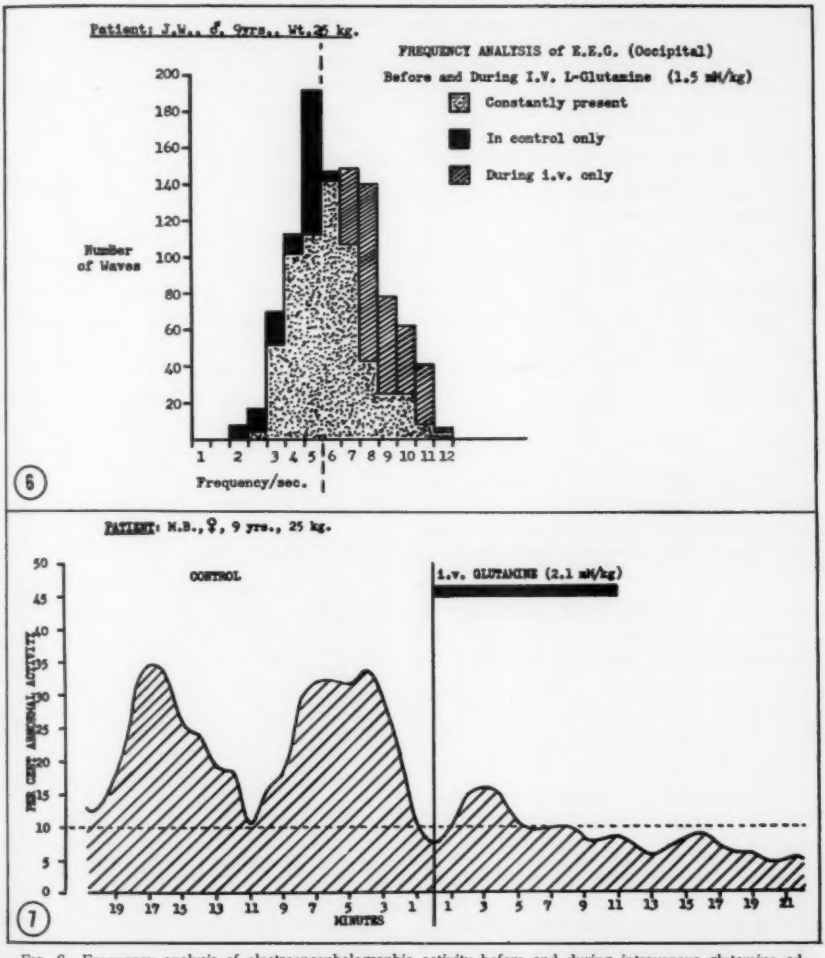


FIG. 6. Frequency analysis of electroencephalographic activity before and during intravenous glutamine administration. Data were derived from records illustrated in figure 4, with only the occipital leads depicted here. The control and infusion periods analyzed were equal in length. All waves in each lead were analyzed for two 10-second runs per minute of recording, and the results have been combined into a composite diagram. For this patient's age the majority of waves would be expected to have frequencies of 6/sec. or higher. The shift to higher frequencies during intravenous glutamine (hatched areas) is statistically significant. (The difference between mean frequencies of control and intravenous periods is statistically stable at less than 0.01 per cent).

FIG. 7. Analysis of the percentage of abnormal electroencephalographic activity per minute of recording before and during intravenous L-glutamine administration in a seizure patient, M. B., female, age 9, weight 25 kg. Dose of L-glutamine 2.1 mM/kg. (7.5 gm.) administered in a total volume of 180 ml. over a period of 15 minutes. Recording conditions were similar to those for figures 4 and 5. Equal durations of the same record were analyzed for control and infusion periods with the percentage of abnormal activity for each minute measured and plotted. The graph illustrated is for occipital leads only and has been smoothed. For this patient 10 per cent abnormal activity would be considered borderline abnormality. The reduction in percentage of abnormal activity during and immediately following the infusion is statistically significant ($P < 0.01$ by the chi-square method).

from the medication regime. The omission was tolerated without incident. Since that time he has enjoyed one period of 15 days without a single seizure. No similar seizure-free period is recorded in the previous three-year period.

Case 2.—The second patient is the nine year old girl previously referred to. She had a premature birth, weighing only 2 lb. 12 oz. at birth, and as an infant was a feeding problem with evident retardation of motor development. Her seizures began at age five years and have been mostly minor in type either as absences or akinetic attacks with infrequent major generalized seizures. On a variety of adequate medications she continued to have an average of at least one minor seizure every three days. She was very introspective, clumsy physically, and could not cope with first grade of school at age eight. At the time of starting her on asparagine 2mM/kg. body weight (7 gm.) four times daily by mouth, all other medication (principally phenobarbital) was abruptly stopped. This change in medication was undergone without incident and in the four months since starting asparagine she has been seizure-free. Her general attitude has changed coincident with this improvement. She is brighter and more self-assured. Her appetite has improved with consequent gain in weight. She now is able to help around the house and play with her sisters for the first time. Schooling has been resumed and consultation with her teachers indicates that her progress is exceeding all anticipation. She is still being maintained seizure-free on asparagine alone.

Other cases. Three other patients are on oral asparagine, but for too short periods to permit conclusions. One is a 36 year old man with probable focal cortical seizures (? left parietal origin) who, on 2 mM/kg. asparagine (14 gm.) four times daily in addition to his previous medications, has experienced such a marked reduction in seizure frequency that he has gone back to work for the first time in over two years. Another is a 19 year old boy with classical petit mal type seizures since the age of five. On all conceivable combinations of medications his seizure frequency has been 50 to 100 per day, necessitating institutionalization. With a dose of 2.5 mM/kg. asparagine (20 gm.) six times daily a substantial, but not dramatic reduction in seizure frequency has occurred with coincidentally a marked improvement in mental attitude. The last patient is a 14 year old boy with seizures of both minor akinetic or absence and major generalized type since age four. The latter occur nocturnally with an average frequency of one to four per night, occasionally rising to as many as ten. Institutionalization has been necessary for this boy. Since adding to his previous medication 2.5 mM/kg. asparagine (12 gm.) five times daily, major seizure frequency has dropped 50 per cent with a substantial reduction in daily minor seizures.

What of the electroencephalographic records which have been closely followed in these patients? Since institution of oral asparagine these have been less easy to interpret. It is an impression that little change occurs in the first six weeks to three months. Thereafter some change is apparent, which is characterized by a greater variability in records taken at frequent intervals. Some records appear to be unchanged in comparison with control records, while others may be definitely or even strikingly improved. Because the electroencephalographic records often may not reflect clinical status, a longer period of assessment on a larger group of patients is desirable before drawing more definite conclusions.

Toxicity

One patient has received over 40 gm. of asparagine intravenously, and another 25 gm. of glutamine. Several patients have consumed in excess of 7 kg. of asparagine by mouth. So far no toxicity or unpleasant side effects have been encountered. All patients on oral asparagine have had frequent reviews of hematologic, renal, and hepatic function and blood nonprotein nitrogen, blood urea nitrogen, and carbon dioxide contents. No deviation from control or normal functions of blood, liver, or kidney systems have occurred. Blood carbon dioxide contents remain within normal

limits. Mild elevations of blood nonprotein nitrogen and of blood urea nitrogen occur regularly, as might be expected by administration of large amounts of a compound which contributes to both of these blood components. The possibility that gastric irritation may be caused by high doses of asparagine was raised in the patient receiving 120 gm. per day, but the failure of the symptoms to persist despite continued administration makes this doubtful. On the basis of experiences so far, it may be stated that no toxicity or side effects occur even with very large doses either intravenously or orally.

Clinical Summary

There are at present nine patients who have received either glutamine or asparagine or both as part of one or other of the two phases of clinical study. No toxic or side effects have been encountered. Transitory, intermittent improvement in electroencephalographic records occurs during intravenous administration of either glutamine or asparagine. After some weeks of oral administration of asparagine, significant clinical improvement occurs and is sustained, but electroencephalographic changes are less clearcut. These results have been obtained in severely involved cases which had responded poorly, if at all, to standard methods of control.

CONCLUSIONS

The cases presented are certainly too few and too early in course to deserve designation as examples of therapy. They are presented rather as an apparent confirmation clinically of results obtained in vitro with glutamine and asparagine on epileptogenic brain tissue. The doses being used are admittedly large. But, being naturally-occurring substances, they sustain dilution on administration and metabolic losses in other tissues. And they must penetrate both the blood-brain barrier and the nerve cell membrane barrier in sufficient concentration to be effective.

The two compounds, glutamine and asparagine, are unique to clinical seizures in several ways. They have no apparent effect in vitro or in vivo on normal nervous tissue function or activity. Thus, they are not drugs in the usual sense of the word. They are naturally occurring compounds, which are normally consumed in the diet and normally present in body fluids and tissues of man. And they are the first compounds administered to seizure patients with promising results, which are based upon an indication derived from metabolic studies on human epileptogenic brain tissue.

Certainly this is not a final answer, but this study exemplifies an approach which may lead to more rational therapy and physiologic control. In addition these investigations provide a better understanding of fundamental mechanisms concerned with neuronal function and acitvity, which may well apply to other still obscure neurologic problems.

The interest and cooperation of the research divisions of Merck and Company, Inc., Rahway, New Jersey in clinical phases of this study has been generous and invaluable. Acknowledgments are also due to Dr. Gertrude Kalz of the department of bacteriology, McGill University, and Dr. Arthur Grieve of Ayerst, McKenna and Harrison, Ltd., Montreal, for assistance in preparation of intravenous solutions used initially in this study. Methionine sulfoximine was kindly supplied by Dr. L. Reiner, Director of Research, Wallace and Tiernan Co., Inc., Belleville, N. J.

REFERENCES

1. Tower, D. B., and Elliott, K. A. C.: Activity of acetylcholine system in human epileptogenic focus, J. Appl. Physiol. 4:669, 1952.
2. Tower, D. B., and Elliott, K. A. C.: Activity of acetylcholine system in cerebral cortex of various unanesthetized mammals, Am. J. Physiol. 168:747, 1952.
3. McIlwain, H.: Electrically excited metabolism of separated mammalian cerebral tissues, EEG & Clin. Neurophysiol. 6:93, 1954.
4. Tower, D. B., and Elliott, K. A. C.: Experimental production and control of an abnormality in acetylcholine metabolism present in epileptogenic cortex, J. Appl. Physiol. 5:375, 1953.
5. Tower, D. B.: Glutamic acid and glutamine metabolism in epileptogenic cerebral cortex, In preparation.
6. Tower, D. B., and Peters, E.: Electrolyte and energy metabolism in epileptogenic cerebral cortex, In preparation.
7. Tower, D. B., and McEachern, D:. Acetylcholine and neuronal activity II. Acetylcholine and cholinesterase activity in the cerebrospinal fluids of patients with epilepsy, Canad. J. Res., E, 27:120, 1949.
8. Elliott, K. A. C., Swank, R. L., and Henderson, N.: Effects of anesthetics and convulsants on acetylcholine content of brain, Am. J. Physiol. 162:469, 1950.
9. MacIntosh, F. C.: Personal communication.
10. Pope, A., Morris, A. A., Jasper, H., Elliott, K. A. C., and Penfield, W.: Histochemical and action potential studies on epileptogenic areas of cerebral cortex in man and the monkey, A. Res. Nerv. & Ment. Dis., Proc. 26:218, 1946.
11. Weil-Malherbe, H.: Significance of glutamic acid for metabolism of nervous tissue, Physiol. Rev. 30:549, 1950.
12. Tower, D. B.: Biochemical abnormalities in epileptogenic cerebral cortex, XIX Internat. Physiol. Congr. Abstr. Communic., 1953, pp. 834-835.
13. Weil-Malherbe, H.: Glutamic acid and its relation to the nervous system, Biochem. Soc. Sympos. 8:16, 1952.
14. Stern, J. R., Eggleston, L. V., Hems, R., and Krebs, H. A.: Accumulation of glutamic acid in isolated brain tissue, Biochem. J. 44:410, 1949.
15. Terner, C., Eggleston, L. V., and Krebs, H. A.: Role of glutamic acid in transport of potassium in brain and retina, Biochem. J. 47:139, 1950.
16. Manery, J. F.: Inorganic Metabolism of Brain, in Biology of Mental Health and Disease, New York, Paul B. Hoeber, Inc., 1952, pp. 124-134.
17. Tower, D. B.: Structural and functional organization of mammalian cerebral cortex: The correlation of neurone density with brain size, J. Comp. Neurol. 101:19, 1954.
18. Pace, J., and McDermott, E. E.: Methionine sulphoximine and some enzyme systems involving glutamine, Nature 169:415, 1952.
19. Speck, J. F.: Enzymatic synthesis of glutamine: A reaction utilizing adenosine triphosphate, J. Biol. Chem. 179:1405, 1949.
20. Gale, W. H.: Studies on the enzymic synthesis of glutamine, Biochem. J. 49:106, 1951.
21. Bessman, S. P., Rossen, J., and Layne, E. C.: γ-Aminobutyric acid-glutamic acid transamination in brain, J. Biol. Chem. 201:385, 1953.
22. Roberts, E.: Personal communication.
23. Haber, C., and Saidel, L.: Glutamic acid in neural activity, Federation Proc. 7:47, 1948.
24. Peters, R. A.: Lethal synthesis, Proc. Roy. Soc., London, s.B. 139:143, 1952.
25. Awapara, J.: The influence of fluoroacetate on the concentration of free amino acids in rat organs, J. Biol. Chem. 197:695, 1952.
26. Coursin, D. B.: Convulsive seizures in infants with pyridoxine-deficient diet, J.A.M.A. 154:406, 1954.
27. Gammon, G. D., and King, G.: Review of recent evidence of the role of pyridoxine in human nutrition, Tr. Am. Neurol. A. 79: In press, 1954.
28. Yoneda, M., and Asano, N.: Competitive action of isonicotinic acid hydrazide and pyridoxal in the amino acid decarboxylation of Escherichia coli, Science 117:277, 1953.
29. Hawkins, J.: Personal communication.
30. Hunt, A. D., Stokes, J., McCrory, W. W., and Stroud, H. H.: Pyridoxine dependency: Report of a case of intractable convulsions in an infant controlled by pyridoxine, Pediatrics 13:140, 1954.
31. Price, J. C., Waelsch, H., and Putnam, T. J.: dl-Glutamic acid hydrochloride in treatment of petit mal and psychomotor seizures, J.A.M.A. 122: 1153, 1943.
32. Schwerin, P., Bessman, S. P., and Waelsch, H.: Uptake of glutamic acid and glutamine by brain and other tissues of rat and mouse, J. Biol. Chem. 184:37, 1950.
33. Kamin, H., and Handler, P.: The metabolism of parenterally administered amino acids, J. Biol. Chem. 188:193, 1951.
34. Tigerman, H., and MacVicar, R.: Glutamine, glutamic acid, ammonia administration and tissue glutamine, J. Biol. Chem. 189:793, 1951.
35. Gale, E. F., and Van Halteren, M. B.: The assimilation of amino acids by bacteria: 13. The effect of certain amino acids on the accumulation of free glutamic acid by *Staphylococcus aureus*: extracellular peptide formation, Biochem. J. 50:34, 1951.
36. Tower, D. B., Courtois, G., and Frost, L. L.: Observations on the administration of L-glutamine and of L-asparagine to experimental animals and to man, In preparation.
37. Alpert, E.: Personal communication.
38. Baldwin, M., Frost, L. L., and Wood, C. D.: Investigation of the primate amygdala: Movements of the face and jaws, Neurology 4:586, 1954.
39. Dawson, R. M. C.: Cerebral amino acids in fluoroacetate-poisoned, anesthetised and hypoglycaemic rats, Biochim. et Biophys. Acta 11:548, 1953.

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D. Section Editor
with the assistance of E. P. Richardson, Jr., M.D.

Presented by *Delbert M. Bergenstal, M.D.,*
Charles F. Barlow, M.D. and Richard B. Richter, M.D.

PRESENTATION OF CASE

A 57 year old white housewife had been in reasonably good health until June 1950. At this time she developed a painfully swollen left wrist. Shortly thereafter similar discomfort appeared in the joints of the fingers, elbows, knees, and ankles. She was hospitalized in December 1950 in the care of her family physician. A positive serology led to the diagnosis of syphilis. She was treated with 4.8 million units of penicillin and subsequently eight weekly injections of bismuth. When released from the hospital she was receiving treatment with cortisone and salicylates. As the arthritic symptoms did not respond she sought treatment at Albert Merritt Billings Hospital. She was admitted to the hospital on the arthritis service in April 1951, where the appropriate joint findings of rheumatoid arthritis were recorded. Further abnormal physical findings included a blood pressure of 192/110 and a systolic murmur. She was found to have positive blood Kahn and Wassermann reactions. Spinal fluid findings were: no white blood cells, total protein 36 mg. per cent, doubtful Wassermann, and colloidal gold curve 3344111000. She was given a course of 15 million units of Procaine penicillin, followed by a course of bismuth salicylate. A diabetic type of glucose tolerance curve was found, but since there was no glycosuria it was felt that insulin therapy was not indicated. The patient was given ACTH in an initial dosage of 80 mg. a day, with gradual reduction to 20 mg., and she experienced considerable relief of the arthritic condition. She was discharged to be followed in the arthritis clinic. By May it was possible to reduce the ACTH to 10 mg. and 5 mg. on alternate days. However, by September she was having more difficulty consisting of pain and tenderness in various joints, and it became necessary to increase ACTH to 20 mg. daily. At this point regular clinic visits stopped and the therapy was largely handled by the patient and her husband. For several days prior to hospital admission in February 1952, she had become increasingly weak to the point of being unable to lift her hands and feet. In addition, she experienced pins and needles sensations in the fingers and was noted to be periodically confused and disoriented. The husband stated that she had received 20 mg. ACTH a day regularly except for four days in the week before admission. Urine, which had tested persistently blue, was orange two days before admission. On physical examination the patient was confused, disoriented, and appeared acutely ill. Blood pressure was 200/110, pulse 96, respirations 24, and temperature 37° C. There was blotchy brown pigmentation over the arms, legs, and face, accompanied by some facial edema, especially in the periorbital area. The patient was "moon-faced" and generally obese. The chest was clear and a harsh systolic heart murmur was heard at the apex, transmitted faintly along the left sternum. There was swelling and tenderness of both hands with marked swelling in the left wrist and some ulnar deviation in the digits of both hands. There was

From the department of medicine and the division of neurology, University of Chicago Clinics, Chicago.

moderate limitation of passive motion in the hips and knees.

On neurologic examination she was found to be unaware of the day and was unable to sustain attention for tests of intelligence and calculation. No abnormality of cranial nerve function was detected. Her speech was slightly slurred, but tongue and pharyngeal movements were normal. There was advanced weakness of all extremities. Weakness was most marked in the lower extremities and more profound distally than in the proximal musculature. Tendon jerks were symmetrical, greatly reduced in the upper extremities, and absent in the legs. The plantar response was flexor bilaterally. All modalities of sensation were defective in a glove and stocking distribution. There were no meningeal signs.

Admission urinalysis was normal except for 3+ reduction; the blood sugar was 280 mg. per cent; the patient was mildly acidotic; CO_2 was 15.6 mM/L. Hematologic examination revealed: white blood count 12,050 with 78 polymorphonuclear cells, hemoglobin 10.5 gm., red blood count 3.82 million, sedimentation rate 18 mm. Repeated urinalysis revealed no microscopic abnormality and no more than a slight trace of albumin. The albumin-globulin ratio was reversed, with the albumin 3.32 and globulin 4.2 gm. per cent. Nonprotein nitrogen was 34 mg. per cent. Blood Kahn reaction was negative. The spinal fluid showed 20 white cells, 34 mg. per cent protein, a negative Wassermann, and a colloidal gold curve of 1122332100.

On admission the patient was treated for diabetic acidosis with insulin and appropriate fluids. The electrolyte balance was restored and the hyperglycemia controlled. The patient remained confused and continued to complain bitterly of pain in the extremities on attempted movement. She was given no ACTH or cortisone during the terminal hospitalization. A course of 19 injections of vitamin B_{12}, 1000 micrograms per day, was given with no benefit. During the third week in the hospital, she developed a peculiar vasomotor reactivity. Each pinprick in attempts to draw blood was followed by prolonged blanching. She eventually developed cyanosis and subsequent dry gangrene of the third and fifth digits of the left hand. Priscoline was given to alter this phenomenon but was of no avail. She developed areas of cutaneous pressure necrosis over the sacrum and ischial tuberosities, and ulceration of the pinnae and of the left anterior tibia. She had occasional spikes of fever which were unexplained and continued despite Chloromycetin, Terramycin, and eventually streptomycin. Her general condition gradually worsened, she became unresponsive, and tube feedings were necessary. She expired quietly on March 12, after a brief period of coma.

DISCUSSION

DR. DELBERT BERGENSTAL (Attending physician): This case was a quite complicated one, for the patient had a number of different disease processes which could singly or in combination present a most varied clinical picture. When she was first seen at Albert Merritt Billings Hospital, the physical findings were those of classical acute rheumatoid arthritis. There was active synovitis in many joints with the typical fusiform, hot, boggy, tender swelling of the joints. The laboratory findings of an elevated sedimentation rate and an increased plasma globulin level were also compatible with this diagnosis.

Attempts to control this inflammatory synovitis with conventional management using aspirin, heat, rest, and physiotherapy were unsuccessful. It was felt that adequate relief could be obtained by using ACTH therapy. There were, however, at least two relative medical contraindications. One was hypertension which seemed to be an essential hypertension without evidence of cardiac or renal failure. The second contraindication involved an interesting problem regarding her carbohydrate metabolism. She stated that no one in her or her husband's family had had diabetes mellitus. Her daughter, however, had had severe juvenile diabetes mellitus with rapidly progressive renal and ocular changes. The patient had tested her urine on frequent occasions and always found it to be negative. Nevertheless, an oral glucose tolerance test done before administering ACTH showed a typical diabetic curve.

She was started on 80 mg. of ACTH a day in divided doses, and this was gradually reduced to 20 mg. per day over a period of one week. This dosage of 20 mg. was continued to the time of her discharge. Following ACTH administration she noted dramatic relief of pain, swelling, and stiff-

ness in her joints, and she was able to walk up and down stairs without difficulty. There was no significant increase in her blood pressure above that of the already existing hypertension. The diabetes mellitus became manifest in that she began to show 1+ to 2+ reduction in the urine. While she was on the higher doses of the ACTH, the blood sugars occasionally rose to levels of 200 mg. per cent in the postprandial periods. When she was on the 20 mg. of ACTH per day, the total loss of carbohydrate in a 24-hour urine specimen was rather small; it was felt that diet management would be adequate to control the diabetes mellitus.

For the next three months she felt fine and ACTH was reduced to 10 mg. and 5 mg. on alternate days. In September there was evidence of renewed activity, and the dosage of ACTH was increased to 20 mg. per day with some improvement in symptoms. From this time to her final admission the patient did not return to the clinic and her therapy was handled by the patient and her husband. There were periods when, for financial reasons, the patient received no ACTH, and these were associated with acute exacerbations of her synovitis.

In February 1952 she developed weakness in the hands and feet, and there were periods of disorientation. The diabetes mellitus was now out of control, and she was acutely ill at the time of admission. There was the classic Cushing facies frequently seen in patients who have required prolonged steroid therapy. The rheumatoid synovitis and muscle spasm were extremely active. She was in a state of exacerbation of her inflammatory arthritis far more severe than had been present at the beginning of ACTH therapy. Despite the prolonged ACTH therapy there were evidences of advanced joint changes and ulnar deviation of the fingers. The other classic findings have been described in the history. The diabetic acidosis was quickly controlled, electrolyte balance restored, and ACTH was discontinued.

Our interpretation of the clinical findings was that the patient was in an acute exacerbation of her rheumatoid arthritis and the weakness and neuropathy were probably secondary to a diabetic neuritis; the mental confusion could have been related to ACTH administration. The interesting development of the very severe vasospasms most clearly seen following attempts at finger puncture for blood sugars and the subsequent development of large gangrenous areas of skin on the fingers, buttocks, and tibia were puzzling and unanswered. Dr. Henry T. Ricketts, who saw the patient, commented on the fact that the geographical distribution of the gangrene over the tibia and the thigh areas did not fit the common picture of diabetic gangrene. The joint findings were those of an acute synovitis which became more severe when ACTH was discontinued.

The continuation of a diabetic neuropathy following control of diabetes mellitus is quite common. The rather rapid progression of the neurologic findings, however, does not entirely fit the picture of diabetic neuropathy, and the frequently observed elevation of spinal fluid protein in diabetic neuropathy was not present here. The increasing mental confusion following discontinuation of ACTH was also unexpected, for the reversal of central nervous system effects of the adrenal steroids is usually quite prompt once the drug is discontinued. Her therapy was directed toward control of the diabetes and the neuropathy. Attempts were made to provide adequate nutrition despite the difficulties encountered because of the mental confusion and agitation. Her condition gradually deteriorated and she expired 33 days after admission.

DR. R. B. RICHTER (Neurologic consultant): This patient was seen in consultation within a few days of her admission to the hospital. The medical service in charge was interested in an opinion concerning both her mental state and the profound weakness of all extremities, which were new developments and constituted the outstanding fea-

tures of her clinical state at that time. It seemed apparent at once that the mental symptoms of disorientation, dulled perception, inattention, and fluctuating stupor were those of a confusional psychosis, attributable in all probability to some general derangement of cerebral metabolism or circulation rather than to focal or disseminated destructive disease of the brain. The preponderance of rather generalized weakness of the arms and legs distally where there was virtually complete paralysis, the loss of tendon reflexes, and the distal glove and stocking impairment of cutaneous sensation in all limbs left no doubt that the patient had severe sensorimotor polyneuritis.

Because none of the well-known conditions such as intoxication with organic solvents, alcoholism, other severe deficiency states, acute infection, or porphyria, in which polyneuritis and toxic psychosis are often associated, appeared to be present, an attempt was made to find an explanation for both in the known elements of the patient's medical background. These were rather confusing in their diversity and included typical rheumatoid arthritis treated with ACTH for many months, syphilis treated intensively, diabetes mellitus, and hypertension. It was thought that the polyneuritis could best be explained as atypical diabetic neuropathy, atypical both in the severity of the paralysis and the degree of involvement of the upper extremities. The confusional psychosis could be adequately accounted for either by cerebral circulatory deficiency incidental to the hypertension, or by the prolonged treatment with ACTH, or possibly by a combination of both with the diabetic acidosis. The question had been raised on several occasions whether the patient's psychosis was not actually caused by cerebral syphilis. I felt quite confident that this was not the case. The nature of the psychosis, the lack of neurologic signs of neurosyphilis, the recent very intensive treatment, and the spinal fluid findings all seem to exclude active cerebral syphilis. It should be said that it was never possible to establish the accuracy of the spinal fluid cell count.

The original diagnostic impression, then, was that of diabetic neuropathy and a nonspecific toxic confusional physchosis.

DR. CHARLES BARLOW (Neuropathologist): The general postmortem examination revealed a number of points of interest. The patient had rheumatoid arthritis with appropriate synovial thickening and a chronic active synovitis. The ascending aorta was the site of a fusiform dilatation and microscopic examination revealed the findings of a luetic aortitis. There was no valvular disease, however. She had a marked septic splenitis and cultures grew *Staphylococcus albus* and *B. proteus*.

The most prominent feature in the general postmortem study was a rather generalized polyarteritis. The histologic details of the arteritis will be discussed in reference to the peripheral nerves, as the arteritis was quite similar in all areas of the body. The arteries of the skeletal muscle were relatively heavily involved and there was considerable atrophy, waxy degeneration, and focal necrosis of muscle fibers. The synovia, gastrointestinal tract, and mesentery were also involved. The arteries of the skin underlying the pigmented areas of the skin were particularly thickened and scarred, and there was increased pigmentation in the overlying melanoblasts.

Gross examination of the brain and spinal cord revealed no important abnormality. It was felt that the brain was unusually pale, both on external examination and on serial coronal sections through the cerebrum, brainstem, and cerebellum. This was the only noteworthy change.

From the standpoint of the nervous system, however, the most crucial pathologic changes were found in the vasa nervorum of the peripheral nerves and in the nerve bundles of the cauda equina. The findings here, as in the general autopsy material, consisted of an arteritis in various stages of development and repair. The arteritis was restricted to arterioles. The arteries of large

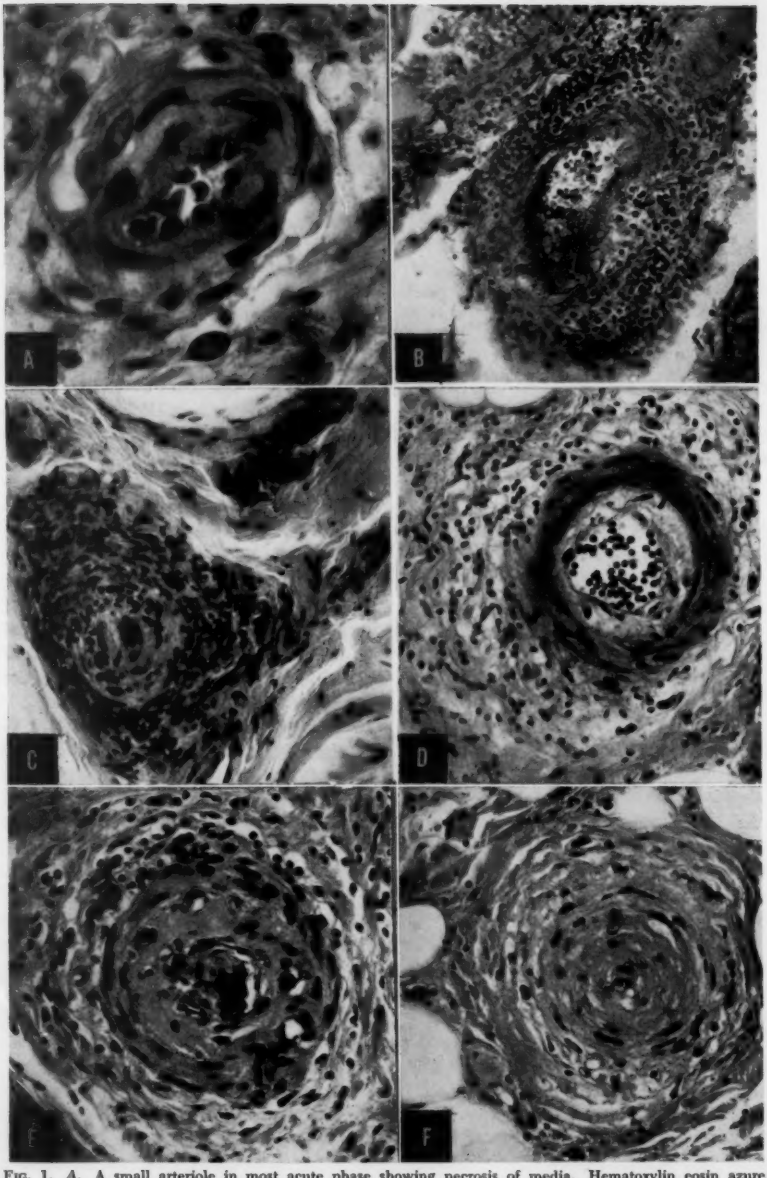


FIG. 1. *A.* A small arteriole in most acute phase showing necrosis of media. Hematoxylin eosin azure stain. *B.* Phase of acute inflammation. Phosphotungstic acid hematoxylin. *C.* Phase of acute inflammation with thrombus formation. Hematoxylin eosin azure stain. *D.* Phase of early granulation tissue formation. This artery demonstrates mild intimal proliferation and the perivascular inflammation is much reduced. Hematoxylin eosin azure stain. *E.* Late phase of granulation tissue formation with evidence of recanalization. Hematoxylin eosin azure stain. *F.* Phase of scar formation. Hematoxylin eosin azure stain.

caliber were normal and no abnormalities were observed in the capillaries. Very rarely one saw a vein surounded by a loose infiltration of inflammatory cells, but this phenomenon was invariably associated with an adjacent actively involved artery and presumably represented spread of the inflammation rather than direct involvement of the vein.

The distribution and intensity of the lesions was of interest. Portions of sciatic and peroneal nerves were available and in these peripheral nerves the process was most widespread and advanced. It was rare to find a normal artery in these preparations and in most sections none was seen. In the nerve roots of the cauda equina the arteritis was not as widespread nor had it been as destructive. In addition, there was some tendency for the more acute stages of arteritis to predominate as opposed to the more frequent finding of chronic scarred vessels in the peripheral nerves. Only two involved arteries were seen in association with the sacral spinal cord. Both arteries were in intimate association with an entering spinal root and lay within the subarachnoid space. No further instances of abnormal vessels were discovered in either spinal or cerebral meninges. No affected arteries were discovered within the substance of the central nervous system, either spinal cord or brain.

The most noteworthy point about the arterial lesions themselves was their variability in terms of chronicity. This point is made repeatedly in the literature of this subject. This variability is mentioned in the general reports of periarteritis nodosa as well as those more specifically describing the nervous system. Lesions varying from the most acute changes which have been described to instances of essentially complete fibrous replacement or "healing" were observed in this case. Great variation was seen from artery to artery in a single section, even when they lay side by side.

Discussion as to the phase of the process in a given artery in this case is in essential agreement with the opinion of Arkin. The most acute alteration consisted of edema and hyalin necrosis predominantly involving the media (figure 1A). The muscle cells were swollen or had disappeared. The endothelial cells were prominent and swollen. This very acute change was actually seen infrequently in the sections examined. A phase of acute inflammation was much more frequently observed (figures 1B and C). It was here that one encountered considerable cellular infiltration of the media and adventitia. The cells largely consisted of lymphocytes and plasma cells with occasional polymorphonuclear leukocytes and large epithelioid cells. Polymorphonuclear leukocytes were relatively inconspicuous in the inflammatory response in this case, suggesting that the most brisk inflammatory phase had largely passed. No eosinophils were seen. The media and adventitia were edematous and often there was considerable swelling and proliferation of the subintima. In rare instances obliteration of the lumen by thrombus had occurred. No instances of aneurysm were observed. The various stages of granulation tissue formation were well illustrated (figures 1D and E). This was probably the most common phase encountered. The inflammatory cells were considerably reduced in number and consisted of lymphocytes and plasma cells. One saw early fibrous replacement of the destroyed media and many thrombi were present. Furthermore, there was a distinct increase in fibroblasts of the adventitia. The considerable proliferation of intima was more advanced in arteries in this phase. The healed stage was well represented (figure 1F). The entire vessel and former lumen was replaced by indifferent fibrous scar, generally poor in nuclei. Occasionally there had been some recanalization of the lumen.

The involved arteries were located in the endoneurium and perineurium, and in one instance within a nerve bundle itself. The epineural and perineural fibrous connective tissue was perhaps slightly excessive, but this was not marked. The structure of the peripheral nerve was profoundly

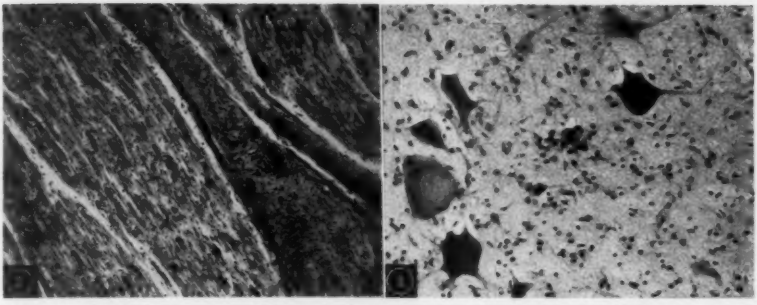


FIG. 2. Longitudinal section of sciatic nerve showing extensive demyelinization. Klüver stain. FIG. 3. Axonal reaction in anterior horn cells of spinal cord. Note focal glial nodule. Cresyl violet stain.

disturbed. In some areas it appeared that there was almost complete tissue destruction with replacement by fibrous tissue. The most usual change, as demonstrated in hematoxylin-eosin-azure preparations, was marked proliferation of Schwann cells accompanied by an accumulation of debris laden macrophages. No discrete infarcts such as have been reported in the literature were observed in this case. Myelin preparations demonstrate loss and active disintegration of myelin (figure 2). The partially preserved myelin sheaths were scattered at random throughout the nerve bundles, and were swollen, fragmented, and occasionally beaded. Sections of cauda equina exhibited distinctly less pronounced alteration of neural integrity. Considerably more intact sheaths were present and there was less evidence of active disintegration. In general the extent of demyelination correlated well with the arteritis. It was distinctly more prominent in peripheral nerves and less evident in the cauda equina. There was certainly nothing here to contradict the general opinion in the literature that the neuropathy is largely due to ischemia as a consequence of the arterial lesions.

The spinal cord at all levels examined showed striking retrograde axonal reaction in the anterior horn cells (figure 3). The cell bodies were swollen and the nuclei eccentric. There was central chromatolysis with only a thin rim of intact Nissl substance. In rare instances the cell had completely disintegrated and a few examples of well-defined neuronophagia were found. The spinal cord was otherwise normal.

The only abnormality discovered in the blocks removed from the brainstem and cerebrum was acute nonspecific retrogressive alteration of cortical neurons. The change seen was mainly swelling and chromatolysis.

DR. BERGENSTAL: The microscopic diagnosis of polyarteritis at autopsy certainly clarified some of the puzzling problems that were encountered during the patient's last hospitalization. The group of so-called connective tissue diseases are frequently related in both their clinical symptoms and laboratory findings, and it is, at times, only with difficulty that a specific diagnosis can be made. All too often, as in this case, the symptoms are those of an acute rheumatoid arthritis; then as the case was followed, the evidence of a more generalized arteriolitis with visceral and neurologic manifestation becomes manifest. Whether the original process was initially a rheumatoid arthritis which transcended into the polyarteritis group of connective tissue diseases or whether the synovitis was an initial manifestation of the polyarteritis is not known. I would favor the former explanation. There was no history of any contact substance which could have acted as a sensitizing agent to produce a polyarteritis. Thus, in

any patient who has rheumatoid arthritis as a manifestation of one of the connective tissue diseases, one must always be on the alert for the development of a more generalized connective tissue disease such as polyarteritis or lupus erythematosus with their highly variable clinical pictures.

DR. RICHTER: It is very easy, of course, to be wise in retrospect after Dr. Barlow's clear cut demonstration of the real nature of the disease in the nervous system, but I would like to say, speaking as a neurologist, that while my erroneous diagnosis might have been excusable 15 or 20 years ago, it is hardly so today. As Dr. Bergenstal has indicated, the real clues to the correct diagnosis were the Raynaud-like symptoms and the vascular trophic changes in the skin, but there were other good hints before this, the most obtrusive being the fact that the patient was known to be suffering from a more benign form of connective tissue disease, rheumatoid arthritis. This alone should have been a compelling reason to carry out a skin-muscle biopsy with good chances of establishing a diagnosis.

It is commonly stated in the literature that the majority of the cases of polyarteritis in which peripheral nerves are affected manifest themselves as a mononeuritis multiplex with successive involvement of various spinal nerves, rather than with the massive simultaneous involvement of many peripheral nerves as is the case with toxic or infectious polyneuropathy. In this patient the rule, if it is a rule, did not hold. The comment has been made that an erroneous diagnosis in cases of polyarteritis nodosa is frequently a diagnosis of an atypical form of some more common condition. This was precisely the pitfall here. A neuritis of a kind not usually seen in uncomplicated diabetes was accepted as diabetic merely because diabetic neuropathy is so common. One should be more wary and not conclude too readily that polyneuritis is alcoholic or diabetic simply because the patient is alcoholic or diabetic. I am reminded of another patient, a diabetic of long standing, who developed advanced polyneuritis of the arms and legs with well marked paralysis and sensory loss much like the present case. It was only after facial diplegia and mental confusion also appeared that I realized that this could scarcely be diabetic neuropathy. The way was then open to make the correct diagnosis which was acute porphyria.

The exact basis for the patient's psychosis remains an unsettled matter. It may be that the original speculations about this were correct. One can only say that many patients who are seriously ill with polyarteritis exhibit various symptoms of toxic psychosis. Some of them, to be sure, have the typical vascular changes in the brain but more often there are no such lesions to account for the mental disorder.

CASE REPORT

Status Marmoratus of the Thalamus and Striatum

Associated with Athetosis and Dystonia

Malcolm B. Carpenter, M.D.*

In 1896 Anton[1] described in detail a case of double athetosis in which abnormal myelinated fibers were found throughout the posterior halves of the putamina. Fifteen years later Oppenheim and Vogt[2] and Freund and Vogt[3] published similar clinicopathologic cases and distinguished them as an entity under the name état marbré or status marmoratus. In the same year Vogt[4] considered the syndrome of the corpus striatum to be characterized by athetoid activity, spasmodic laughing and crying, variable degrees of paresis, and intellectual deterioration. Subsequent studies have shown that status marmoratus is the most common etiology of double athetosis.[5–8] Status dysmyelinisatus (état dysmyelinique), a closely related condition, has been reported in a few cases,[5,6,9,10] but is considered rare. The relationship between these pathologic conditions has not been clearly established, though they sometimes occur together. Vascular necrotizing lesions of the striatum and/or pallidum are not infrequently reported in cases of athetosis.[11–15]

The original contention of the Vogts that status marmoratus was a "pure striatal syndrome" has not been substantiated by subsequent studies. Status marmoratus of the striatum and thalamus has been described,[6,9,16,17,18] and cortical fibromyelin plaques in addition to status marmoratus of the striatum have been reported.[5,17,19,20,21,22] That athetosis is not inevitably associated with marbling of the striatum is attested by other authors' findings.[20–25] Status marmoratus of the thalamus without involvement of the striatum or globus pallidus is unusual. Norman[26] reported this finding in a five year old child who died of scarlet fever. Birth was said to have been premature, traumatic, and associated with asphyxia. The child was physically and

From the department of anatomy, College of Physicians and Surgeons, Columbia University, New York City.

*John and Mary R. Markle Scholar in Medical Science.

This material was made available for study through the cooperation of the departments of neurology and pathology (division of neuropathology) of Columbia University and the Neurological Institute of Presbyterian Hospital.

mentally retarded and had convulsive seizures, but no athetoid activity was described. In studying normal thalami, Alexander noted that the dorsomedial nuclei occasionally had a marbled appearance and remarked on the surprising number of individual differences in the myeloarchitectural pattern of the normal thalamus.

In the following case athetoid and dystonic activity was associated with status marmoratus, which was of a severe degree in the thalamus and involved the putamen to a lesser extent.

CASE REPORT

First admission: A 22 year old male was first admitted to the Neurological Institute at his own request on January 22, 1942, with a chief complaint of generalized abnormal involuntary movements. Birth was said to have been premature (exact duration of the pregnancy was unknown), traumatic, and instrumental. The extent and nature of birth injuries were unknown; birth weight was five pounds. Resuscitation was difficult during the first three or four hours of life and questionable convulsions occurred during the first few days after delivery. The child was considered normal by the parents until about two years of age when jerking movements developed in all parts of the body. As the child grew older the abnormal involuntary movements were said to have increased. The child sat unaided at one and a half years, stood unaided at four years, talked at five years, and walked alone at seven years. When the patient was about 15 years old he felt that his condition was improved and that he was able to talk and walk better than at any previous time. The left side of the body was considered weaker than the right and abnormal activity was most marked on that side. The abnormal involuntary activity was aggravated by excitement, emotional stimulation, and observation by other people; it was improved by quiet surroundings and ceased during sleep. The "nervousness" of the entire body could not be controlled voluntarily, even with great effort. When the patient walked his whole body writhed so that he had great difficulty keeping his balance. Although he sometimes stumbled in walking, he almost never fell. The patient was never able to write or to execute any skilled movements with his hands. He had considerable difficulty feeding and dressing himself. The patient complained of sensations of stiffness in his muscles most of the time. He perspired easily, but did not seem to tire readily on physical exertion. There had never been any difficulty in swallowing. The patient did not attend school until he was 13 years old because the schools would not accept him; he left school at age 18, at which time he was in the fifth grade. He earned a poor living as a card salesman. The past history and family history were unremarkable.

Examination: The patient was alert, well oriented, and cooperative. The general physical examination was essentially within normal limits. Neurologic examination showed the following significant findings: In the standing position the feet were spread apart, and the trunk tilted forwards on the pelvis. The gait was unsteady with a scissors quality and a tendency towards oversteppage. Although torsion of the trunk was observed, no bizarre posturing or contortions were noted. Athetoid activity was present in the muscles of the face, neck, and all extremities. Muscle tone seemed somewhat increased throughout the body, but no localized weakness was detectable. The deep tendon reflexes were moderately active and approximately equal on the two sides. Equivocal extensor toe responses were elicited bilaterally. Nonequilibratory tests of coordination were performed slowly and clumsily; rapid successive movements were poorly performed bilaterally. The patient was unable to stand on either foot alone. The appreciation of all sensory modalities was apparently intact, though some observers considered that there was some reduction in sensation on the left side of the body. Speech was slow, thick, dysarthric, and at times explosive. Action potentials of irregular amplitudes and frequency without synchronization were found on electromyography. These were considered to be typical of athetosis and dystonia. On psychometric study (Wechsler-Bellevue) the intelligence quotient was 77. After reviewing the case, the neurosurgeons felt that the patient would not be benefited by surgery and he was discharged as unimproved on January 30, 1942.

Second admission: On October 22, 1947 the patient (then age 27) was readmitted, again at his own request, for reconsideration of advisability of surgical treatment. The neurologic findings were essentially the same as on the first admission. Laboratory data were within normal limits. On October 24, 1947, a laminectomy from C-1 to C-4 was

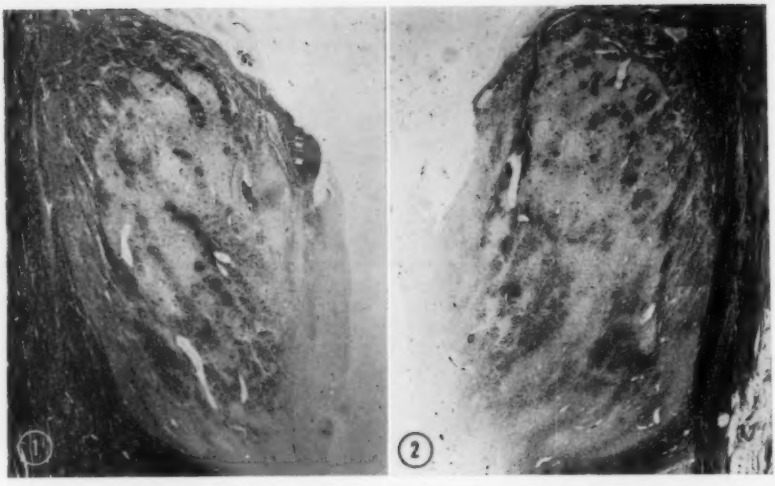
performed and the anterior roots of the first three cervical roots were sectioned bilaterally. A left ventrolateral cordotomy was performed at C-4 by electrocoagulation. Following surgery the patient had a complete tetraplegia and cessation of all abnormal involuntary movements. On the third postoperative day the patient developed an elevated temperature and signs of atelectasis on the left. In spite of chemotherapy the temperature rose to 108° F. on the seventh postoperative day and the patient expired.

Autopsy: The brain appeared symmetric, with long narrow cerebral hemispheres and a normal gyral pattern; it weighed 1,680 gm. The external appearance of the cerebellum and brainstem was normal, though the brainstem seemed somewhat small in comparison to the large cerebral hemispheres. The cranial nerves were normal. The blood vessels at the base of the brain appeared normal, except for some smallness of caliber.

Coronal sections of the cerebrum revealed that the thalami were firm, pallid, and striated by bands of irregular whitish tissue which coalesced in places to form white patches of variable size. In most areas these striations produced a reticulated or lacy appearance. This effect extended from the rostral portions of the thalami, where it was somewhat diffuse, to the pulvinar of both sides, where it had a more homogeneous appearance. This process was asymmetric, being more marked on the right anteriorly and on the left posteriorly. The anterior and medial thalamic nuclei were involved, but not as extensively as the lateral nuclear groups. The medial third of the posterior portion of the head of the right caudate nucleus was pallid. Faint marbling was present in the putamina; the globus pallidus of both hemispheres appeared grossly normal. The rostrum of the corpus callosum was malformed and consisted of only a thin membrane. The body and tail of the caudate nuclei in the region of the stria terminalis had a grayish-white appearance similar to that seen in the thalamus. Gross sections of the cerebellum did not appear abnormal. The brainstem was normal on sectioning, except for questionable pallor of the substantia nigra. No reduction in the size of the cerebral peduncles was noted. At the operative site the cervical dura was somewhat thickened and a small amount of hemorrhage was evident. The color, contour, and consistency of the spinal cord were normal, except for some decreased resistance in the region of the fourth cervical segment. On sectioning the spinal cord at the operative site, some lack of clarity in the demarcation between gray and white matter was noted and some localized softening and faint discoloration were apparent in the left ventral and lateral funiculi, as well as in the zone of the anterior horn. The remainder of the spinal cord was normal.

Microscopic examination: Sections taken from the right superior frontal, left superior and middle frontal, right central and left calcarine gyri were stained with hematoxylin and eosin. With the exception of some mild congestion of the leptomeninges, cortical edema, and hyperemia, these sections were normal. A number of ependymal granulations and denuded ependymal cells in a few areas was found in sections taken from the left hippocampus. Mahon stained sections of the basal ganglia revealed that the caudate nuclei were normal in size and configuration. Normal straight radiating myelinated fiber bundles coursed through the heads of the caudate nuclei. Cells of the caudate nuclei (Nissl stain) were normal in number, size, and morphology. The putamina were traversed by more than the usual number of compact fiber bands, as well as by interlacing myelinated fibers distributed irregularly and coursing through the usual striations at random angles. As a result the contrast between the striations and the ground substance were not as sharp as usual. Classic marmoratic areas were seen throughout the putamina. In Nissl stained sections of the putamina there appeared to be some slight reduction in the number of large and small cells, particularly the latter in the right putamen. In the Mahon stained sections of the globus pallidus, interlacing bands of neural fibers seemed somewhat increased in numbers, though the size and configuration of this structure was normal. The cellular structure of the pallida was essentially normal, except for some cells which seemed pale. The internal capsule was not remarkable.

The most extensive alterations were found in the thalami. Marbling throughout the lateral thalamic nuclei bilaterally with sparing of the reticular nuclei was conspicuous in the Mahon stained sections. Many broad bands of neural fibers traversed the lateral thalamic nuclei in an interlacing fashion, subdividing it into irregular islands, and producing the marbling effect. Nissl stained sections of the thalami revealed some distortion of cellular groups in and around areas occupied by supernumerary bundles of myelinated fibers and gave the impression of neuron loss. Small isolated groups of neu-



FIGS. 1 AND 2. Photomicrographs of sections through the right and left thalami demonstrating intense marbling. Mahon stain.

rons appeared compressed by the myelinated fiber bundles, while other groups were diluted by their presence. Conspicuous cellular loss was not evident. No glial proliferation was apparent in the sections of the thalamus stained with Mallory's phosphotungstic acid hematoxylin. In Bodian stained sections there were additional bands of fibers in the thalami and putamina composed of axons of apparently normal caliber and staining properties.

Small scattered perivascular hemorrhages of recent origin, probably agonal, were found in sections through the third ventricle and hypothalamus. The paraventricular and supraoptic nuclei appeared well preserved. In sections of the diencephalon and mesencephalon, the subthalamic nuclei, red nuclei, substantia nigra, and cerebral peduncles were within normal limits, as were the other nuclei and fiber tracts. The pons and medulla, including the medullary reticular substance, were unremarkable except for congestion of the leptomeninges. Sections of the cerebellar cortex and deep cerebellar nuclei were unremarkable.

Examination of the operative area of the spinal cord: In sections of the fourth cervical segment of the spinal cord there was a wedge-shaped area of destruction in the ventral part of the lateral column on the left which did not extend to the central gray. Intense edema was noted in surrounding areas. The posterior portions of both dorsal columns were destroyed in part, the columns of Goll being most affected. One large area of fresh hemorrhage occupied the outer portion of the central gray at the junction of the posterior and lateral horns, while fresh petechial hemorrhages were scattered throughout both anterior horns. Additional irregular areas of degeneration in the posterior columns and on the surface of the right lateral column were found in Mahon stained sections. The posterior roots were partially degenerated. In Nissl stained sections there was acute degeneration of the anterior horn cells bilaterally, but most pronounced on the left; remaining cells were swollen and lacking in cytologic detail. Other portions of the spinal cord examined were within normal limits.

The findings in the remainder of the autopsy were unremarkable except for the lungs, where patchy groups of alveoli were filled with red blood cells and a pink protein precipitate. Congested capillaries containing numerous polymorphonuclear leukocytes and large mononuclear cells were present in the interalveolar septae.

Summary of pathologic findings: Grossly the brain appeared large and symmetric, with a normal gyral pattern. On sectioning the cerebrum the thalami were firm, pale,

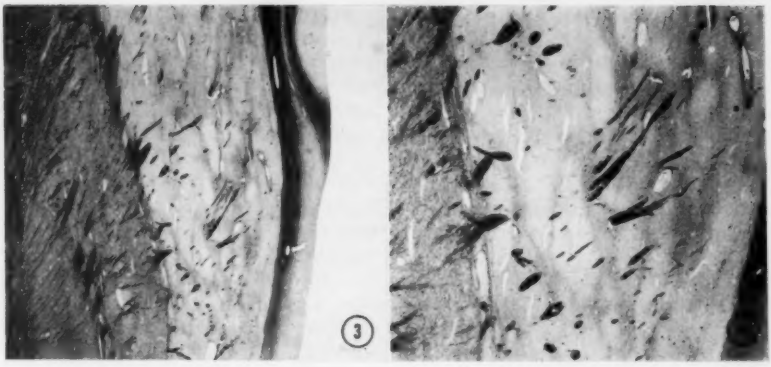


FIG. 3. Photomicrograph of the left putamen showing less intense marbling than was observed in the thalami. Mahon stain.

FIG. 4. Photomicrograh of left putamen, higher magnification. Mahon stain.

and presented a white patchy appearance; this process was asymmetric but involved all major nuclear groups. The putamina also appeared pale and faintly mottled; the pallida were grossly normal. The posterior portion of the head of the right caudate nucleus and the body of both caudate nuclei were firm and grayish-white. The rostrum of the corpus callosum was atrophic.

Microscopic examination of the thalami and putamina revealed interlacing bands of fine myelinated fibers passing in a random fashion which subdivided these structures into irregular islands of varying density, thus producing a marbled appearance. The marbling effect was most pronounced in the thalami. Nissl stained sections showed no conspicuous cellular loss in these structures or in the caudate nuclei. No glial proliferation was apparent in the thalami, caudate nuclei, putamina, or pallida. Mahon stained sections of the pallida revealed some increase in myelinated fibers, but the cellular structure was essentially normal. Sections taken from various portions of the brainstem and cerebellum were within normal limits.

DISCUSSION

The cause of a status marmoratus has never been elucidated. Although originally interpreted as a congenital malformation, subsequent observers have considered it to be due to birth trauma,[9, 21, 22, 24, 26–33] and/or infantile febrile illness;[16, 23–25] hereditary factors have also been cited[1, 5, 27, 28] as the cause. Alexander[21] preferred to call the condition the "status marmoratus anomaly" since his studies led him to conclude that the marbling fibers were normal myelinated nerve fibers, which for some unknown reason had taken an aberrant course. He considered that these fibers were probably frontopontine fibers which left the internal capsule to infiltrate the striatum, and in some cases the thalamus and pallidum. As evidence he cited the normal histologic appearance and staining properties of the aberrant bundles in Weigert, Marchi, and silver stained preparations, as well as in unstained preparations studied in polarized light. The marbling fibers did not seem to alter the course or appearance of the normal radiating striatal bundles and differed from them only in their irregular distribution and looseness of arrangement. In sections through the pons, marked reduction or attenuation of the frontopontine fibers without associated alteration of pontine nuclei was described. In those cases of status marmoratus with involvement of the thalamus striking attenuation of the fiber content of the medullary reticular substance was said

to have been noted. Information regarding the state of the frontopontine tracts in the peduncles and the mesencephalic reticular substance was conspicuously lacking in his report. Most authors are in agreement concerning the normal staining properties and histologic appearance of the marbling fibers. However, in silver stained preparations Bielschowsky[19] observed degenerated myelin sheaths and thickening of the axis cylinders. Christensen and Stubbe Teglbjàerg[35] likewise reported that some of the myelin sheaths had undergone degenerative changes in their case. Bielschowsky felt that there was myelination of neurofibrils which were normally not myelinated and that this process was brought about by pronounced glial (presumably he was referring to oligodendroglia) proliferation in the affected areas. Denny-Brown[7] supported this conclusion and remarked that, "deposition of myelin is a function of glia." This disorder was considered by him to be a "specific variety of gliosis" attended by deposition of myelin. Case[23] reported status marmoratus in a child of four years and remarked, "my case seemed to have an encephalitic background as do all those more recently described." Similar cases could not be found. Using Spielmeyer's and Holzer's stains he found areas of gliosis and hypermyelinization to be unrelated.

Conspicuous atrophy or shrinkage of the striatum was found in the cases reported by Anton,[1] Oppenheim and Vogt,[2] Freund and Vogt,[3] Scholz,[27] and Christensen and Stubbe Teglbjàerg.[35] Although reductions of both large and small striatal cells have been found by most authors, the small striatal cells appear most affected.[9, 17, 19, 27–29] Christensen and Stubbe Teglbjàerg, however, found the large cells reduced in number. Increases in small glial cells have been found by numerous observers, usually scattered in small groups and sometimes in areas corresponding to those occupied by abnormal myelin fibers. Meyer[16] reported the case of a seven year old child in which proliferating glial cells and fibers were present about thickened blood vessels and concluded that vascular changes were the primary cause of the phenomenon. Alexander was unable to find significant striatal cellular changes in his cases, sections of which were stained by Nissl, Mallory's phosphotungstic acid hematoxylin, and Masson's trichrome methods. Microincineration of the striatum revealed a normal ash picture.

The present case is of particular interest because status marmoratus involved the thalami to a greater extent than the striata and these findings were associated with athetosis and dystonia. Pathologic changes in the striatum consisted of fine irregularly dispersed myelin fibers in addition to the normal radiating bundles. Striatal atrophy was minimal. Marked marbling of the thalami, particularly the lateral nuclear groups without glial proliferation, was seen. No apparent reduction of the frontopontine fibers was evident in sections of the mesencephalon and pons, a finding at variance with the postulated theory of Alexander. Norman[21, 22, 26] has advanced the theory that status marmoratus is a late sequel to vascular disturbances and anoxia occurring during abnormal parturition. The incidence of birth trauma and/or significant birth complications (for example, artificially induced labor, instrumental delivery, precipitous labor, premature birth, difficult and protracted labor, severe asphyxia, jaundice, and convulsions soon after birth) has been estimated to be present in the histories of at least 50 per cent of cases.[8] In the cases reported by Byers[31] definite birth injury was established in nine of the ten cases; three of these cases were subsequently studied pathologically by Alexander. Status marmoratus of the striatum

and thalamus has been found in association with other cerebral pathology (for example, cystic cavitation, diffuse patchy devastation of cortical layers, leptomeningeal fibrosis, brain atrophy, ventricular enlargement, and areas of central necrosis and demyelinization) said to be consistent with and directly attributable to birth trauma.[20–22, 26, 30, 33] Double athetosis was not present in many of these cases, presumably because of the extensive nature of coexisting pathology. An extreme example is that cited by Juba[24] in which diffuse multiloculated polyporencephaly and bilateral thalamic atrophy were found in addition to état marbré of the striati. Norman has concluded that état marbré is probably a late sequel to vascular lesions occurring during abnormal birth from venous stasis and anoxia. The distribution of the marmoratic areas in the striatum and thalamus in most reported cases does not conform in any apparent way with known patterns of venous drainage. Certainly status marmoratus does not usually present a periventricular distribution, as one might expect from interference with the Galenic venous system.[36,37] Although there appears to be some evidence that this condition is associated with birth injury or complication and certain theories regarding its pathogenesis, the origin of the abundant, diffuse, loosely arranged marbling fibers remains an enigma.

The most interesting feature of the present case was the extensive nature of the extrapyramidal symptoms associated with the marmoratic phenomenon which involved the thalamus to a greater extent than the putamen. Cases of athetosis[6, 9, 16, 17, 18, 22] associated with status marmoratus of the striatum and thalamus have been reported, but in these cases the striatum was the site of the most marked marbling. Alexander states that the thalamus is the second most frequent site of marbling, followed by the globus pallidus and the cerebral cortex. Neither athetosis or dystonia occurred in the cases of status marmoratus of the striatum and thalamus described by Löwenburg and Malamud, or in the case reported by Norman in which the thalamus alone was involved.

SUMMARY

A case of status marmoratus of the thalamus and striatum with athetosis and dystonia is reported. Birth was traumatic, instrumental, premature, and complicated by difficulty in resuscitation. Athetosis and dystonia became apparent during early infancy and were not progressive; intelligence was in the range of low normal. Postmortem pathologic examination revealed classic status marmoratus of the thalamus and striatum, being somewhat more marked in the former structure. No conspicuous cellular loss or glial proliferation was apparent in these structures. This case was considered unusual because the thalamus was involved by the marmoratic process to a greater extent than the putamen.

The author acknowledges with sincere thanks the helpful criticism and suggestions of Dr. Abner Wolf, who made this material available for study.

REFERENCES

1. Anton, G.: Ueber die Beteiligung der basalen Gehirnganglion bei Bewegungsstörungen insbesondere bei chorea, Jahrb. f. Psychiat. 14: 141, 1896.
2. Oppenheim, H., and Vogt, C.: Nature et localisation de la paralysie pseudobulbaire congenitale et infantile, J. f. Psychol. und Neurol. 18:293, 1911.
3. Freund, C. S., and Vogt, C.: Ein neuer Fall von Etat marbré des Corpus striatum, J. f. Psychol. u. Neurol. 18:489, 1911.
4. Vogt, C.: Quelques considération générales a propos du syndrome du corps strié, J. f. Psychol. u. Neurol. 18:479, 1911.
5. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striaren Systeme, J. f. Psychol. u. Neurol. 25:627, 1920.
6. Alexander, L.: The fundamental types of

histopathological changes encountered in cases of athetosis and paralysis agitans, A. Res. Nerv. & Ment. Dis., Proc. 21:334, 1942.

7. Denny-Brown, D.: Diseases of the Basal Ganglia and Subthalamic Nuclei, Oxford University Press, New York, 1946, pp. 29-39.
8. Carpenter, M. B.: Athetosis and the basal ganglia, Arch. Neurol. & Psychiat. 63:875, 1950.
9. Onari, K.: Ueber zwei klinische und anatomische kompliziert liegende Fälle von Status marmoratus des Striatum, Ztschr. Neurol. u. Psychiat. 98:457, 1925.
10. Kreyenberg, G.: Status dysmelinisatus des Pallidum bei congenitaler bilateraler Athetose, Ztschr. Neurol. u. Psychiat. 132:806, 1931.
11. Fischer, O.: Zur Frage der anatomischen Grundlage der Athetose double und der posthemiplegischen Bewegungsstörung überhaupt, Ztschr. Neurol. u. Psychiat. 7:463, 1911.
12. Scharapow, B. I. and Tschernomordik, P. M.: Zur Pathologie der Stammganglien, J. f. Psychol. u. Neurol. 35:279, 1928.
13. Papez, J. W., Hertzman, J., and Rundles, R. W.: Athetosis and pallidal deficiency, Arch. Neurol. & Psychiat. 40:789, 1938.
14. Crothers, B., and Cobb, S.: Progressive athetosis with lesions in basal ganglion: A case, New England J. Med. 203:213, 1930.
15. Neustaedter, M.: Choreo-athetosis and athetosis (clinicopathologic report), Dis. Nerv. System 4:6, 1943.
16. Meyer, A.: Zur Auffassung des Status marmoratus, Ztschr. Neurol. u. Psychiat. 100:529, 1926.
17. Gozzano, M.: Studio anatomo-clinico di un caso di atetosi doppia, Riv. pat. nerv. 43:41, 1934.
18. Holzer, R.: Ueber das Vorkommen des Status marmoratus im Thalamus opticus, Ztschr. Neurol. u. Psychiat. 151:696, 1934.
19. Bielschowsky, M.: Ueber den Status marmoratus des Striatum und atypische Markfasergeflechte der Hirnrinde, J. f. Psychol. u. Neurol. 31:125, 1924.
20. Norman, R. M.: An example of status marmoratus of the cerebral cortex, J. Neurol., Neurosurg. & Psychiat. 1:7, 1938.
21. Norman, R. M.: Atrophic sclerosis of the cerebral cortex associated with birth injury, Arch. Dis. Childhood 19:111, 1944.
22. Norman, R. M.: Etat marbré of the corpus striatum following birth injury, J. Neurol., Neurosurg. & Psychiat. 10:12, 1947.
23. Case, T. J.: Status marmoratus related to early encephalitis, Arch. Neurol. & Psychiat. 31:817, 1934.
24. Juba, A.: Ueber eine frühenfantile Grosshirnmissbildung (Polyporencephalie und Status marmoratus), Ztschr. Neurol. u. Psychiat. 157: 622, 1937.
25. Löwenberg, K., and Malamud, W.: Status marmoratus, Arch. Neurol. & Psychiat. 29:104, 1933.
26. Norman, R. M.: Etat marbré of the thalamus following birth injury, Brain 72:83, 1949.
27. Scholz, W.: Zur kenntnis des Status marmoratus, Ztschr. Neurol. u. Psychiat. 88:355, 1924.
28. Van Bogaert, L.: Sur une varieté non décrite d'affection familiale: L'epilepsie myoclonique avec choreo-athétose, Rev. neurol. 52:385, 1929.
29. Pfeiffer, F.: Chorea-Athetose bei der Little-Lähmung, Arch. Psychiat. 72:728, 1925.
30. Pfeiffer, F.: Ein besonderer Fall von "Status marmoratus," Psychiat.-neurol. Wchnschr. 41: 409, 1939.
31. Byers, R. K.: Discussion of paper by Alexander, L., see reference 6.
32. Meyer, A., and Cook, L. C.: Etat marbré, J. Neurol. and Psychopath. 16:341, 1935.
33. Benda, C. E.: The late effects of cerebral birth injuries, Medicine 24:71, 1945.
34. Jakob, A.: The anatomy, clinical syndromes, and physiology of the extrapyramidal system, Arch. Neurol. & Psychiat. 13:596, 1925.
35. Christensen, E., and Stubbe Teglbjaerg, H. P.: Double athetosis with status marmoratus, Acta psychiat. et neurol. 21:177, 1946.
36. Schwartz, P.: Erkrankungen des Zentralnervensystems nach traumatischer Geburtsschädigung. Ztschr. Neurol. u. Psychiat. 90:263, 1924.
37. Alexander, L.: The vascular supply of the strio-pallidum, A. Res. Nerv. & Ment. Dis., Proc. 21:71, 1941.

Neurology

BOOK REVIEWS

The Human Diencephalon. A summary of development, structure, function, and pathology.

Hartwig Kuhlenbeck, M.D., Ph.D. 1954. Basel and New York: S. Karger. 230 pages, 33 illustrations.

THIS compact and attractively published monograph on the structurally most complex, clinically puzzling, and experimentally least accessible region of the forebrain is, as its subtitle indicates, a summary. However, the summary is replete with interesting new information, much of which has come to light only recently and is not as yet widely current among neurologists. The account of the morphologic development, structure, and connections of the dorsal and ventral thalamus, of the pretectal region, and of the hypothalamus represent the bulk of the material of the monograph.

This strictly morphologic section is most authoritatively documented from the author's long personal experience and first-hand knowledge of the subject. The monograph opens with a concise and comprehensive discussion of the fundamental morphologic pattern of the organization of the wall of the prosencephalic vesicle in four longitudinally arranged zones from which the epithalamus, the dorsal thalamus, the ventral thalamus, and the hypothalamus differentiate. On the basis of this new and original concept of the longitudinal zones the author gives a detailed description of the nuclei of the dorsal thalamus in the classification of which he conforms to the current nomenclature, but often departs from the more current notions in his interpretation of their morphology and grouping. He includes into the thalamus the diencephalic part of the pretectal region and gives an instructive account of the nuclei and fiber connections of this difficult and poorly explored transitional zone between the thalamus and the tectum mesencephali.

The most interesting and somewhat daring departure from the generally held notions is found in the author's treatment of the hypothalamus, into which he incorporates the subthalamic region and the pallidum. Instructive discussions of the neurohypophysis and of the hypophysioportal system, of the subependymal cell plate, and of the neurosecretory organs of the third ventricle are extremely valuable sections of the book for a general reader. The anatomic section of the monograph is admirable in the precision and lucidity with which the author treats his subject. The simple and clear diagrams and low power microphotographs of the more critical and representative sections of the diencephalon illustrate the text.

The sections of the monograph dealing with functional aspects of the various diencephalic structures and fiber connections appear to take a second place in the composition of the monograph. These parts consist of a synthesizing summary

of the more recent developments in the experimental physiology of this region of the forebrain. The review of these developments is adapted for the needs of presentation of the morphologic data. The material is most ingeniously woven into the context of the morphologic information presented and is often thought provoking; such are the chapters on reverberating and self re-exciting circuits and on the anatomic substrata of consciousness and of pain experience.

As should be expected in a monograph dealing primarily with development and morphology, the clinical symptomatology and pathology of the human diencephalon are considered rather briefly and in a somewhat summary fashion. Nevertheless, in this reviewer's opinion, the book will be most specially useful to many clinical neurologists and neuropathologists who, in their routine dealing with clinical problems, still live by the anatomic cliches cast two generations ago and who want to be brought up to date on the anatomy and physiology of the so-called "basal ganglia."

P. I. Y.

The National Hospital, Queen Square, 1860-1948.

Gordon Holmes, M.D., F.R.S. 1954. London and Edinburgh: E. & S. Livingstone, Ltd. Baltimore: The Williams & Wilkins Co. 98 pages. $3.00.

IN THE PREFACE to his history of the National Hospital, Queen Square, Sir Gordon Holmes states, "The publication of a history of this institution, small and without the claims of age that many of Londons' hospitals have, is justified not only by the quality of the work done, and the contributions to medical knowledge made therein, but also by the interest and affection it has aroused in those who worked there in any capacity or visited it. One can claim that its influence on that branch of medicine with which it deals has spread through most of the civilized world, wherever its students have carried its practice and teaching." Everyone working in the field of neurology today will reaffirm these statements. The National Hospital, through the work of Jackson, Gowers, Bastian, Brown-Séquard, Collier, Buzzard, Horsley and many others, including the distinguished group of men working there today, has been the place of birth and development of British neurology, perhaps the outstanding school of neurology in the world today. American neurology has derived more from the British than from any other school of this discipline, and there is scarcely an American neurologist who does not feel a bond of kinship and affection for Queen Square.

This small book tells the fascinating story of the progress of this hospital from a single ward in a private house to a center of neurology known all over the world. Its foundation was wholly due to the efforts of Miss Johanna Chandler, a middle-aged woman of moderate means. Through her energy and appeals for help, however, funds were gathered and the "National Hospital for the Relief and Cure of the Paralysed and Epileptic" was opened in June 1860. From its earliest days emphasis has been placed on the importance of teaching, with the ultimate establishment of the Institute of Neurology, affiliated with the British Postgraduate Medical Federation and the University of London.

Sir Gordon Holmes not only depicts the birth, adolescence, and eventual maturation of the National Hospital, but also briefly commemorates the names and achievements of the physicians and surgeons who raised it to its present eminence. It is fortunate for those interested in diseases of the nervous system that the author, one of the most distinguished neurologists of all time, has seen fit, in his retirement, to write this splendid volume – an outstanding contribution to the history of neurology.

R. N. DE J.

NEWSLETTER

FEBRUARY, 1955

Howard D. Fabing, President
Walter O. Klingman, President-Elect
Francis M. Forster, Vice-President
Alexander T. Ross, Secretary
Dave B. Ruskin, Treasurer

AMERICAN ACADEMY OF NEUROLOGY

National Meetings Held in New York From December 9 to December 14, 1954, New York City provided the traditional setting for a series of professional meetings concerned with the nervous system, beginning with the annual meeting of the American League Against Epilepsy and terminating with examinations of the American Board of Psychiatry and Neurology. The Epilepsy League, which met in the Ambassador Hotel (December 9), besides providing a stimulating scientific program, also highlighted a special luncheon and press conference for the recent investigations on "Epilepsy and the Law" by Roscoe L. Barrow, dean of the Cincinnati University College of Law, and Howard D. Fabing, Academy president.... Following the epilepsy sessions, the 34th annual meeting of the Association for Research in Nervous and Mental Disease began its program at the Roosevelt Hotel (December 10-11). The central topic for discussion was the neurologic and psychiatric aspects of disorders in childhood, and included in the program was a paper on the present status of the poliomyelitis problem by Dr. Jonas Salk.... The final meeting of the series was the annual examination of the American Board, held at the New York Neurological and Psychiatric Institutes of Columbia University College of Physicians and Surgeons. (The list of new diplomates will appear in the March Newsletter.).... The newly elected presidents of the above societies are: Dr. Russell N. DeJong of Ann Arbor, (Epilepsy League); Dr. J. E. Moore of Baltimore (ARNMD); and Dr. Kenneth E. Appel, Philadelphia (American Board of P & N).

International Conference in Myasthenia Gravis On December 8, 1954, in the School of Medicine of the University of Pennsylvania, an international conference on myasthenia gravis was held under the auspices of the Myasthenia Gravis Foundation. After a note of welcome from Dr. John McK. Mitchell, dean of the School of Medicine, University of Pennsylvania, 20 revealing scientific papers were presented on the fundamental and clinical aspects of myasthenia gravis. The scientific sessions were opened by Henry R. Viets on the problem posed by this disorder and was followed by intense discussions on such subjects as neuromuscular transmission; the role of the thymus in myasthenia; myasthenia and the endocrine glands; and current

drug therapy and management of myasthenia gravis. Special emphasis was given to the structure of the motor endplate and the concentration of choline esterase in this organ (Nastuk and Koelle); the influence of cations on myasthenic muscles (G. Milton Shy); the relationship of decamethonium to curare (Churchill-Davidson, St. Thomas Hospital, London, England); the depolarizing effect of the choline radical (Grob and Harvey); the relationship of the action potential fatigue and fatigue as measured by the isometric ergometrogram (Botelho); the indications for thymectomy (Eaton); the problem of myasthenic and cholinergic crises (Tether); and the relative therapeutic value of Tensilon, WIN 8077, and Mestinon. These and other provocative topics formed the basis of lively discussion and a profitable meeting.... George D. Gammon, professor of clinical neurology at Pennsylvania, who was instrumental in planning the program, provided the final summary of the discussions.

Symposium on Neurology Held in Richmond

A symposium on neurology constituted the program of the 26th annual Stuart McGuire Lecture Series of the department of continuation education at the Medical College of Virginia (December 1-3, 1954). The program included lectures on vascular diseases of the brain, vascular lesions of the pituitary gland, cerebral complications of myocardial infarction, cluster headache, and acute infantile hemiplegia. The 26th annual McGuire Lecturer was Raymond D. Adams, and among other visiting lecturers were C. T. Vicale, E. Charles Kunkle, Walter O. Klingman, David Clark, and O. Rhett Talbert.

* * * * * *

Aging is Subject for ARNMD Meeting in 1955

The neurologic and psychiatric aspects of the disorders of aging will be the topic of the 35th annual meeting of the Association for Research in Nervous and Mental Disease, to take place at the Hotel Roosevelt in New York (December 9-10, 1955), according to its president, Dr. J. E. Moore of Baltimore. The program committee consists of J. E. Moore, chairman; H. Houston Merritt, John Romano, David Seegal, Nathan Shock, and John C. Whitehorn. In general, the first day will be devoted to the discussion of basic information and the second to clinical problems of aging.

New Program in Neurology at State University of New York

A new training program in neurology has been established at the College of Medicine at New York City, State University of New York, according to A. M. Rabiner, professor of neurology and director of the neurologic service at Kings County

Hospital. This program has a large bed service in neurology at Kings County Hospital, where there are also facilities in neuropathology, neurophysiology, and neurochemistry. The service is closely integrated with the neurosurgical service where Jefferson Browder is director of neurosurgery. Candidates are now being considered for full time teaching positions in this expanding program, an associate professor in neurology, an instructor in neurology, and an assistant instructor in neurology. Also there are several additional appointments available for residencies on the neurologic service at Kings County Hospital beginning July 1, 1955.

Epilepsy Clinic Established at Indiana Medical Center Alexander T. Ross, Academy secretary and chairman of the department of neurology, Indiana University Medical Center, reports that an epilepsy clinic is being established at the Indiana University Medical Center as a result of a grant of $15,372 from the James Whitcomb Riley Memorial Foundation. While the prime interest of the clinic will be centered in children, it also will provide service to adult seizure patients. It is planned that the clinic will be under the major supervision of Dr. Philip T. White, who also will be in charge of teaching and research activities.

* * * * * *

Expanded Graduate Training Program Announced at Northwestern Benjamin Boshes, chairman of the department of neurology and psychiatry, Northwestern University Medical School, announces a graduate training program in neurology for residents and fellows at Northwestern University Center for Graduate Training. This program, which carries a three-year board approval, is designed for a rotating type of training in neurology, the first year being spent at a large general hospital with extensive neurologic, neurosurgical, and psychiatric services. The second year is spent at the VA Hines Hospital which has a 225 bed neurologic service and a 250 bed special unit for patients with spinal cord injuries or disease. The third year is spent at the VA Research Hospital on the campus of Northwestern which has a 24 bed neurologic service. The program includes complete courses in the basic neurologic sciences, ranging from neuroanatomy to EEG and EMG. Individuals on the program may work toward the degree of M.S. or Ph.D. in neurology. Sufficient training also is offered in psychiatric conditions to enable the individual to manage these conditions on a clinical, teaching, or research level. Each training year starts in July 1st. Salaries, which begin at $2400 per year, are increased during the three years. All communications or inquiries should be forwarded to Dr. Benjamin Boshes, Chairman, Department

of Neurology and Psychiatry, Northwestern University Medical School, Chicago, Ill.

Conference on Cerebral Palsy A three day conference on the treatment of cerebral palsy, organized by the British Council for the Welfare of Spastics, was held in London recently. Americans participating in the meetings included Drs. Winthrop Phelps, Temple Fay, and M. A. Perlstein, president of the American Academy for Cerebral Palsy.... Mr. Wylie McKissock, surgeon to the National Hospital for Nervous Diseases, Queen Square, reported on his results in 35 hemiplegic patients on whom he had performed complete hemispherectomy during the last five years.

Here and There Dr. J. Godwin Greenfield, noted English neurologist and neuropathologist, formerly dean of the Institute of Neurology, National Hospital, Queen Square, London, has joined the staff of NINDB as a visiting scientist for a period of six months.... Paul C. Bucy, professor of neurology and neurologic surgery at the University of Illinois since 1941, has joined the faculty of Northwestern University's Medical School as professor of surgery.... After a continuous career of service since 1926 with the New York State Department of Mental Hygiene, Dr. Armando Ferraro has retired (November 30, 1954) from his position as principal research scientist, neuropathology, at the New York State Psychiatric Institute. On November 24th a farewell party was given in his honor by members of the staff of the Institute, who presented him with airplane luggage as a token of their esteem.... A recent visitor to this country was Prof. Jan Jansen of the University of Oslo, Norway, an international leader in the field of neuroanatomy.... Dr. Kenneth Magee of the University of Michigan has joined the staff of NINDB....

Pearce Bailey

Hoeber-Harper
proudly announces
a new landmark
in the world's neurologic literature

CLINICAL NEUROLOGY

by 65 authorities; edited by
A.B.BAKER, M.D., U. of Minnesota

a reference work in 3 volumes

CONTENTS

1. CASE TAKING AND EXAMINATION
2A. ROENTGENOGRAPHY
2B. ELECTROENCEPHALOGRAPHY AND ELECTROPHYSIOLOGIC METHODS
2C. DIAGNOSTIC OPHTHALMOLOGY
2D. CEREBROSPINAL FLUID
2E. PSYCHOLOGICAL TESTING
3. PHYSIOLOGY OF CEREBRAL LOCALIZATION
4. AGNOSIA, APRAXIA, APHASIA
5. INTRACRANIAL NEOPLASMS
6A. INTRACEREBRAL VASCULAR DISEASE
6B. EXTRACEREBRAL VASCULAR DISEASE
7. CEREBRAL ANOXIA
8. HEADACHE
9. INFECTIONS OF THE DURA
10. MENINGITIS
11. BRAIN ABSCESS
12. VIRAL ENCEPHALITIS
13. SECONDARY ENCEPHALITIS
14. NEUROSYPHILIS
15. CEREBRAL INTOXICATION
16A. DRUG ADDICTION
16B. ALCOHOLISM
17. CRANIOCEREBRAL TRAUMA
18. CONVULSIVE DISORDERS
19. DEMYELINATING DISEASES
20. EXTRAPYRAMIDAL DISEASES
21. HYPOTHALAMUS AND PITUITARY GLAND
22. THE CEREBELLUM
23. DISEASES OF THE BRAIN STEM
24. SPINAL CORD LOCALIZATION
25. SYRINGOMYELIA AND RELATED CONDITIONS
26. SPINAL CORD TUMORS
27. PROTRUDED INTER-VERTEBRAL DISKS
28. VASCULAR DISEASES OF THE SPINAL CORD
29. SPINAL CORD TRAUMA
30. MYELITIS
31. MUSCULAR ATROPHIES AND DYSTROPHIES
32. PERIPHERAL NERVES
33. NEURALGIAS
34. ANOMALIES
35. CONGENITAL DISEASES
36. INFANTILE CEREBRAL PALSY
37. VEGETATIVE NERVOUS SYSTEM
38. VITAMIN DEFICIENCIES
39. ENDOCRINE DISTURBANCES
40. NEUROLOGIC COMPLICATIONS OF INTERNAL DISEASE
41. NEUROLOGIC REHABILITATION
42. PSYCHOLOGIC ASPECTS OF NEUROLOGY
43. GENETIC ASPECTS

After years of planning, writing and editing, this *new* Reference Guide to Neurology is ready. You can now have on your shelf for instant use a 3-volume integrated source of today's knowledge of diagnosis and treatment—including not only the more common neurologic disturbances but also the rarer syndromes and the ramifications of neurology in the fields of internal medicine, pediatrics, endocrinology, psychiatry, ophthalmology and otolaryngology. Attention is focussed throughout on the clinical and therapeutic aspects of the subject. The 65 contributors are recognized authorities on their assigned topics. While the first objective is to organize for practical use the known facts of neurology, much new material is published here for the first time. At left you will see the wealth of detail Baker's *Clinical Neurology* will place at your fingertips. This 3-volume set is destined to become the cornerstone of every serious collection on nervous system disorders and a major part of every reference shelf on general medicine. It will serve you well for years to come.

over 2100 pages • liberally illustrated

to examine this important 3-volume set on approval mail the coupon TODAY

N-1-2

PAUL B. HOEBER, Inc., Publishers
MEDICAL BOOK DEPARTMENT OF HARPER & BROTHERS
49 East 33rd Street, New York 16, New York

Send *on approval* Baker's CLINICAL NEUROLOGY . . . $60.00

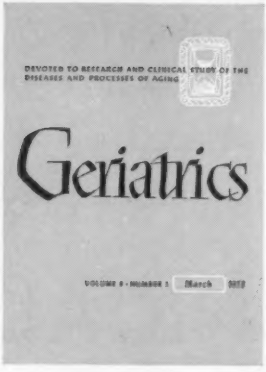
☐ Check Enclosed ☐ I will pay $5.00 per month ☐ Bill me 30 days after delivery

Name.....

Address.....

City..... Zone..... State.....

17A



Who is the geriatric patient?

One of every 3 Americans is, or at any moment may become, a geriatric patient. More than 50,000,000 men and women are now over 45 years old. It is estimated that some 195,000,000 prescriptions will be written this year for patients in this age group. The diseases of these millions of individuals constitute the largest single field of medical research and practice. The doctor seeking to expand his professional knowledge and increase his ability to serve more patients will find it profitable to investigate this ever-growing field.

GERIATRICS gives you latest reports on cardiology, surgery, gynecology, urology, proctology, arteriosclerosis, endocrine problems, arthritis, cancer, nutrition and other aspects of disorders common to middle-aged and older persons. Month by month GERIATRICS brings you a continuing, exhaustive study of clinical, psychological and sociological aspects of this vital field.

GERIATRICS, 84 S. 10th St., Minneapolis 3, Minn.

Enter my subscription for GERIATRICS as indicated below. It is understood that I may cancel this within 10 days after receipt of the first issue if I am not fully satisfied.

☐ 1 year 12 issues $8 ☐ 2 years $12.50
☐ Check enclosed ☐ Bill me later

NAME _____

ADDRESS _____

POSTOFFICE _____ ZONE ____ STATE _____

REVIEW COURSES IN BASIC and CLINICAL NEUROLOGY

APRIL 25, 26, 27, 1955

Preceding the

1955 AMERICAN ACADEMY OF NEUROLOGY MEETING

Shamrock Hotel, Houston, Texas

NEUROPATHOLOGY—April 25, 1955. Dr. Fae Y. Tichy, chairman. Fees: Juniors: $15.00; Fellows, Actives and Associates: $20.00; Non-members: $30.00. Deposit on slide box: $25.00.

NEUROROENTGENOLOGY—April 25, 1955. Dr. A. L. Sahs, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $20.00; Non-members: $25.00.

ELECTROENCEPHALOGRAPHY—April 26, 1955. Dr. V. R. Zarling, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROPHYSIOLOGY—April 26, 1955. Dr. James L. O'Leary, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

THE COLLAGEN DISEASES—April 27, 1955. Dr. Joe R. Brown, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROMUSCULAR DISORDERS—April 27, 1955. Dr. G. Milton Shy, chairman. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

ENROLLMENT FOR ALL COURSES IS LIMITED

Priority will be determined by date of application

•

Outline of each course, application and further information may be obtained from

Mrs. J. C. McKinley, Executive Secretary
3501 East 54th St., Minneapolis 17, Minn.

FOUNDED 1879

RING SANATORIUM

Eight miles from Boston

For the study, care and treatment of emotional, mental, personality and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.

Full resident and associate staff. *Courtesy privileges to qualified physicians.*

BENJAMIN SIMON, M.D.
Director

CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights, Massachusetts

Telephone AR 5-0081

This is the lounge in McFarland Hall, the open unit of Hall-Brooke for convalescent and psychoneurotic patients. Comfortable surroundings are considered important in this modern psychiatric hospital devoted to active treatment, analytically-oriented psychotherapy, and the various somatic therapies.

Hall-Brooke

Greens Farms, BOX *31, Connecticut*
Telephone: Westport, CApital 7-5105

George S. Hughes, M.D., *Medical Director*
Leo H. Berman, M.D., *Clinical Director*

Heide F. Bernard
Samuel Bernard
Administrators

Products and Services . . .

FIND NO MAJOR NEUROLOGIC DAMAGE AFTER 10,098 SPINAL ANESTHESIAS

Results of a study of 8,460 patients given 10,098 spinal anesthetics, one of the largest series to receive "spinals" at one hospital, have revealed no instances of major neurologic damage after postoperative follow-ups of as much as five years. The study was made by Drs. Robert D. Dripps and Leroy D. Vandam at the hospital of the University of Pennsylvania between 1948 and 1951. Based on their findings and other medical data, they term as "unjustified" the tendency "to assume a cause and effect relationship between spinal anesthesia and a variety of complaints, sometimes appearing years after the anesthesia. Our experience indicates that the mortality rate following spinal anesthesia is lower than that recorded after general anesthesia in comparable patients undergoing comparable types of operations."

Of the 10,098 spinal anesthetics administered, almost 75 per cent, 7,127, consisted of Pontocaine. The second most frequently employed agent, procaine, was given 1,399 times. A check made at least six months following 8,987 "spinals" disclosed one instance of incapacitating neurologic disease. This later proved to be due to a spinal cord condition "that prior to spinal anesthesia had caused no recognizable symptom," the authors state, adding the patient subsequently recovered completely.

IMPROVED THERAPY OF MYASTHENIA GRAVIS REPORTED

A new drug is reported to make life more comfortable for sufferers from the rare muscular disease, myasthenia gravis: it is Mestinon, made by Hoffmann-La Roche, Nutley, New Jersey. Mestinon is known chemically as a dimethyl carbamate of 3-hydroxy-1-methyl pyridinium bromide. The doctors say that Mestinon produces far fewer undesirable reactions than neostigmine. These reactions include diarrhea (resulting from increased peristalsis or intestinal contractions), stomach cramps and pains in limb muscles as well as running of the eyes and increased salivation. The new compound is characterized as "a step forward in the search for the ideal drug therapy for myasthenia gravis."

Mestinon is a close chemical relative of neostigmine (Prostigmin), now used as standard treatment for myasthenia victims.

NEW ANTIBIOTICS FOUND IN MOLD OF AUREOMYCIN

The golden-colored mold, Streptomyces aureofaciens, which produces Aureomycin chlortetracycline and Achromycin tetracycline, also produces other antibiotics, it was revealed by scientists of Lederle Laboratories Division,

(Continued on page 23A)

automatically
controlled
SERIAL
angiography

Model 110
Universal
Automatic
Seriograph

Here is automatically controlled serial angiography with highest quality, standard size pictures and standard developing procedures!

Full control by Radiologist permits test pictures and delays during picture cycle. The 12 individual cassettes, each with its own set of screens, give you 11" x 14" (or smaller) standard pictures for adult angiographic studies.

Seriograph operation is equally efficient in the horizontal or vertical position. Automatic time selector gives ½ to 2 second infinitely variable interval.

For details of these and many other outstanding features of the new Model 110 Universal Automatic Seriograph write to:

the **Automatic**
Seriograph Corp.
4910 CALVERT ROAD
COLLEGE PARK, MARYLAND

• The Philadelphia General Hospital offers one year combined residencies in Neuropathology and Clinical Neurology for candidates for certification by the American Boards of Neurologic Surgery, Psychiatry and Neurology. Applicants accepted July 1 and January 1.

For details, apply to:
Office of Medical Education
Philadelphia General Hospital
Philadelphia 4, Pennsylvania

BALDPATE, Inc.

Geo. 2131 **Georgetown, Mass.**

Located in the hills of Essex County, 30 miles north of Boston

For the treatment of
psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment;
electric shock treatments, sub-coma and deep coma insulin therapy when indicated.

Occupation under a trained therapist, diversions and outdoor activities.

G. M. Schlomer, Medical Director

Reg. U.S. Pat. Off.

MEASURE Sensory Changes

The Bio-Thesiometer® enables you to make improved sensory tests because it MEASURES sensory changes. The results are expressed in numbers as they are in measuring blood pressure, temperature or other quantitative tests.

In addition to giving you quantitative and diagnostic data in your first test, owners emphasize "it is also valuable in following the progress of the disease, whether there is improvement or lack of improvement." The Bio-Thesiometer® test replaces qualitative and non-standardized tests of sensation. The results are expressed in relative or absolute units which have exactly the same meaning to all those making such tests. The Bio-Thesiometer® is a new tool for the diagnosis of many conditions in which the nervous system or vascular system is involved. May we send you complete information? Write to

BIO-MEDICAL INSTRUMENT COMPANY
20 Munn Road Newbury, Ohio

SEDATION AND EUPHORIA FOR NERVOUS, IRRITABLE PATIENTS

Use **VALERIANETS-DISPERT** Reg. U. S. Pat. Off.

Each Chocolate Coated Tablet Contains Ext. Valerian (highly concentrated) 0.05 Gm. dispergentized finely subdivided for maximum efficiency

TASTELESS, ODORLESS, NON-DEPRESSANT SEDATIVE and EUPHORIC

VALERIANETS-DISPERT are indicated in cases of nervous excitement and exhaustion, anxiety and depressive states, cardiac and gastrointestinal neuroses, menopausal and menstrual molimena, insomnia

Dose: 1 or 2 tablets t.i.d. — Bottle of 50 and of 100 tablets

At All Prescription Pharmacies

STANDARD PHARMACEUTICAL CO., INC. • 1123 Broadway, New York

For Intestinal Dysfunction
NUCARPON®
Each tablet cont: Extract of Rhubarb, Senna, Precip. Sulfur, Peppermint Oil, Fennel Oil in activated charcoal base.

For making Burow's Solution U.S.P. XIV
WET DRESSING Use
PRESTO-BORO®
(Aluminum Sulfate and Calcium Acetate)
POWDER IN ENVELOPES — TABLETS —

For treatment of Swellings, Inflammations, Sprains

For Pulmonary Conditions
TRANSPULMIN®
3% solution Quinine with 2½% Camphor for Intramuscular Injection

PRODUCTS & SERVICES

(Continued from page 21A)

American Cyanamid Company, Pearl River, New York, in a paper read at the Second Annual Symposium on Antibiotics sponsored by the U. S. Food and Drug Administration in Washington, D. C.

The new antibiotics, as yet unnamed, are an antifungal agent and several antibacterial agents designated as "Activity X." While "Activity X" has been broken down into several components, they have not yet been completely isolated or identified. It was discovered that the antibacterial activity of one component of "Activity X" could be increased significantly by heating.

The selection of a nutrient medium in which the mold grows is apparently the major factor in determining the relative proportions of the antibiotics formed by S. aureofaciens. Media variations resulted in the production of Aureomycin alone, or Aureomycin with greater or lesser amounts of the antifungal agent and "Activity X."

The paper chromatography method was used by the authors, Drs. J. H. Martin, A. J. Shay, L. M. Pruess, J. N. Porter, J. H. Mowat and N. Bohonos, in separating the various antibiotics.

Improved cerebral sedative

LOBICA-DEBRUILLE, INC.
1841 Broadway
New York 23, N. Y.

DETOXICATED SCOPOLAMINE

In relieving rigidity and tremor in paralysis agitans, and in cases of delirium tremens, chronic alcoholism and narcotic addiction —physicians are relying increasingly on GENOSCOPOLAMINE, an improved cerebral sedative, to aid them in their work.

GENOSCOPOLAMINE (scopolamine aminoxide hydrobromide) is highly useful as an amnesic in labor and as preanesthetic medication.

Prolonged sedation of psychic and motive centers is obtained without scopolamine's high toxicity. A pharmacological study* shows that GENOSCOPOLAMINE is only one-sixth as toxic and one-third as potent as ordinary scopolamine.

GENO SCOPOLAMINE

*Am.J.Pharm.—117:319-326, 1945

CARROL TURNER SANATORIUM

MEMPHIS, TENNESSEE, ROUTE 10, BOX 288

For the Diagnosis and Treatment of Mental and Nervous Diseases

Located on the Raleigh-LaGrange Road, five miles east of the city limit—accessible to U. S. Highway 70 (Bristol Highway). Situated on a sixty-six acre tract of wooded land and rolling fields, the environment is conducive to amelioration of the symptoms of emotionally disturbed patients.

Modernly equipped with adequate facilities for physical and hydrotherapy, electroshock, and insulin therapy.

Special emphasis is laid on recreational and occupational therapy

Adequate nursing personnel assures individual attention to each patient.

The main building and hospital department of the Sanatorium is shown above.

FAIRFIELD

Our convalescent home is located on the Sanatorium Grounds

The home is especially designed and fitted for the care of elderly people.

Lederle

Hibicon*

Benzchlorpropamide *Lederle*

ANTICONVULSANT

Effective therapy without drowsiness, lethargy, incoordination, visual disturbances, hypoplastic anemia, agranulocytosis

HIBICON provides effective control of grand mal seizures, often in cases resistant to therapy with other anticonvulsants. No serious toxic reactions have been reported.

Numerous clinicians have reported on the absence of sedative effects and lethargy, and the definite feeling of well-being and heightened morale among patients treated with HIBICON.

HIBICON is supplied in capsule form. The usual dosage is 0.5 Gm. to 1.5 Gm., 3 or 4 times daily, with meals and before retiring.

Available in 250 mg. and 500 mg. capsules, in bottles of 100 and 1,000.

*REG. U. S. PAT. OFF.

LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

PEARL RIVER, NEW YORK

New

Pharmaceutical Elegance

FOR A STANDARD SEDATIVE

LUMINAL® OVOIDS

Distinctive · Sugar Coated · Oval Shaped

Easy Color Identification of Dosage Strength

¼ grain		(yellow)
½ grain		(light green)
1½ grains		(dark green)

Bottles of 100 and 1000

LUMINAL: Pioneer Brand of Phenobarbital

Over 30 Years of Manufacturing and Clinical Experience

Winthrop-Stearns INC.

NEW YORK 18, N. Y. WINDSOR, ONT.